

Building graphical and computational models in Systems Biology

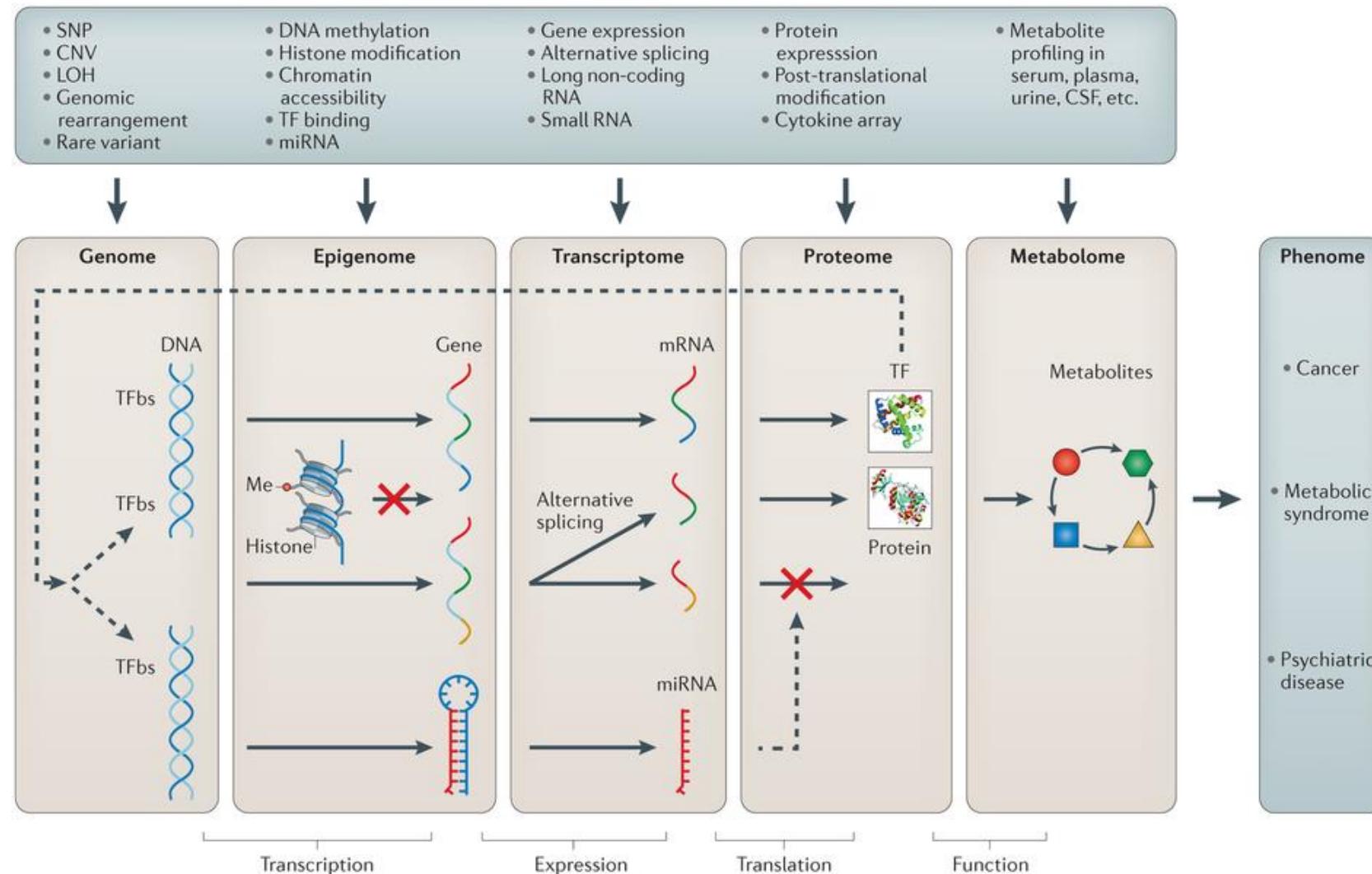
WTAC

Computational Systems Biology for Complex Human Disease

Dr Anna Niarakis

Hinxton Campus, Monday 5th December 2022

Organisms: Complex systems

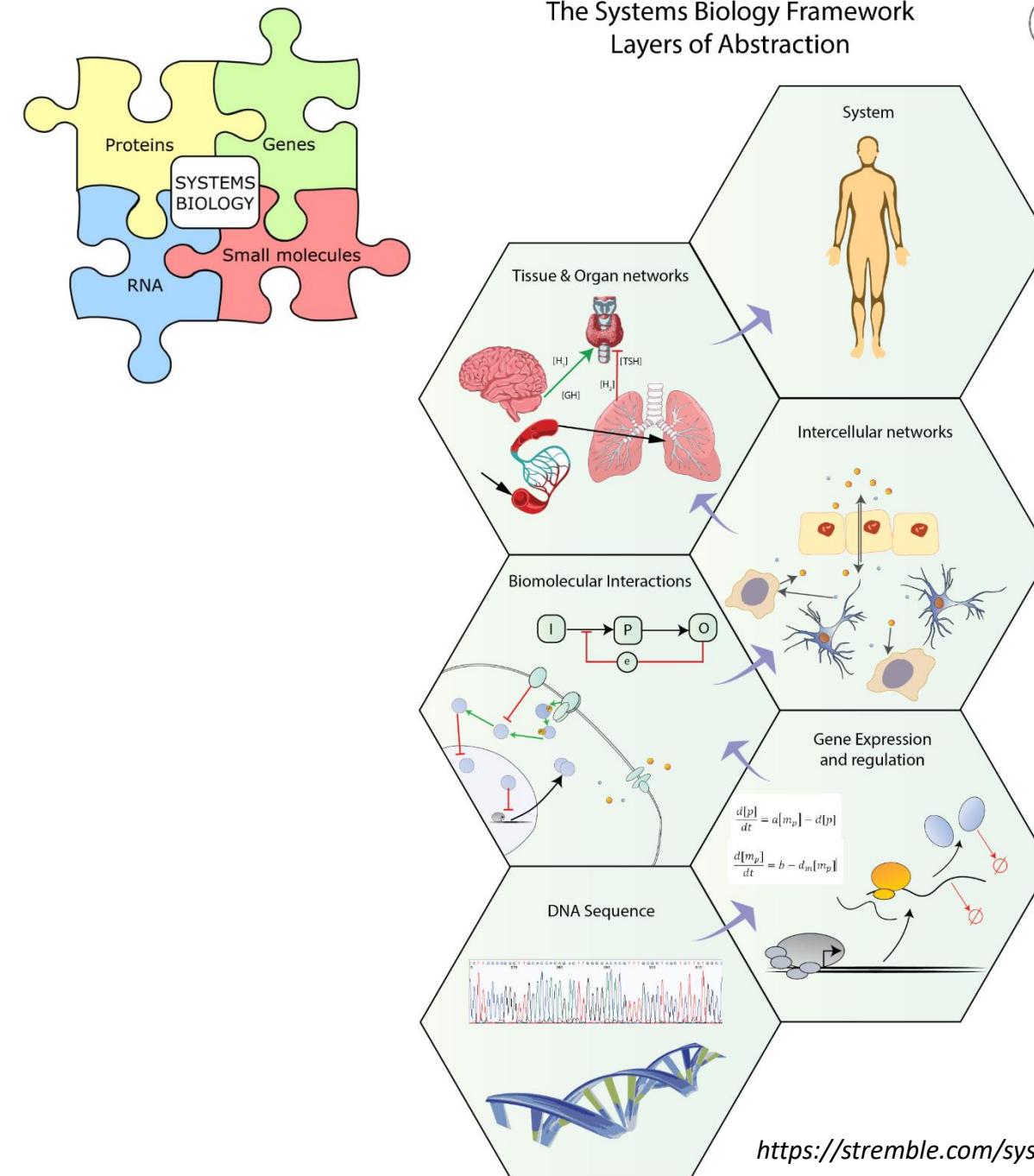


Systems biology: put bits and pieces together

How do the individual parts interact
to yield system behavior?

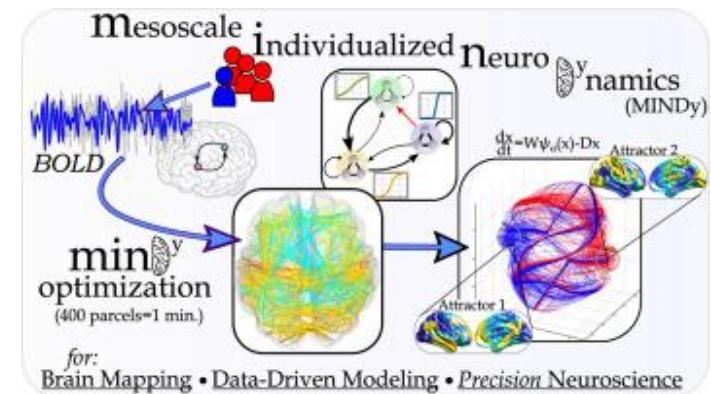
Biology has focused on figuring out
the pieces.

But what happens when you fit
them together?

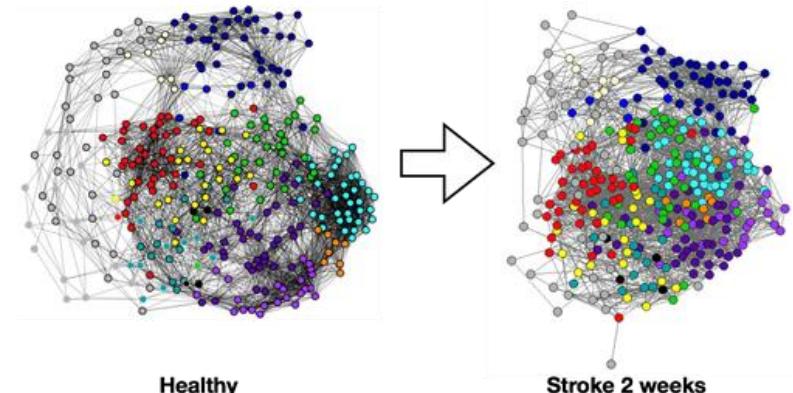


The concept of model in science

- A physical, mathematical, graphical, logical, conceptual, computational representation of an object, event or process or a system of objects, events or processes.
- Abstraction of the « real thing ».
- Helps us study and understand the **system** of interest and the **mechanisms** under which it operates.
- Can also lead to predictions about the system's behaviour.

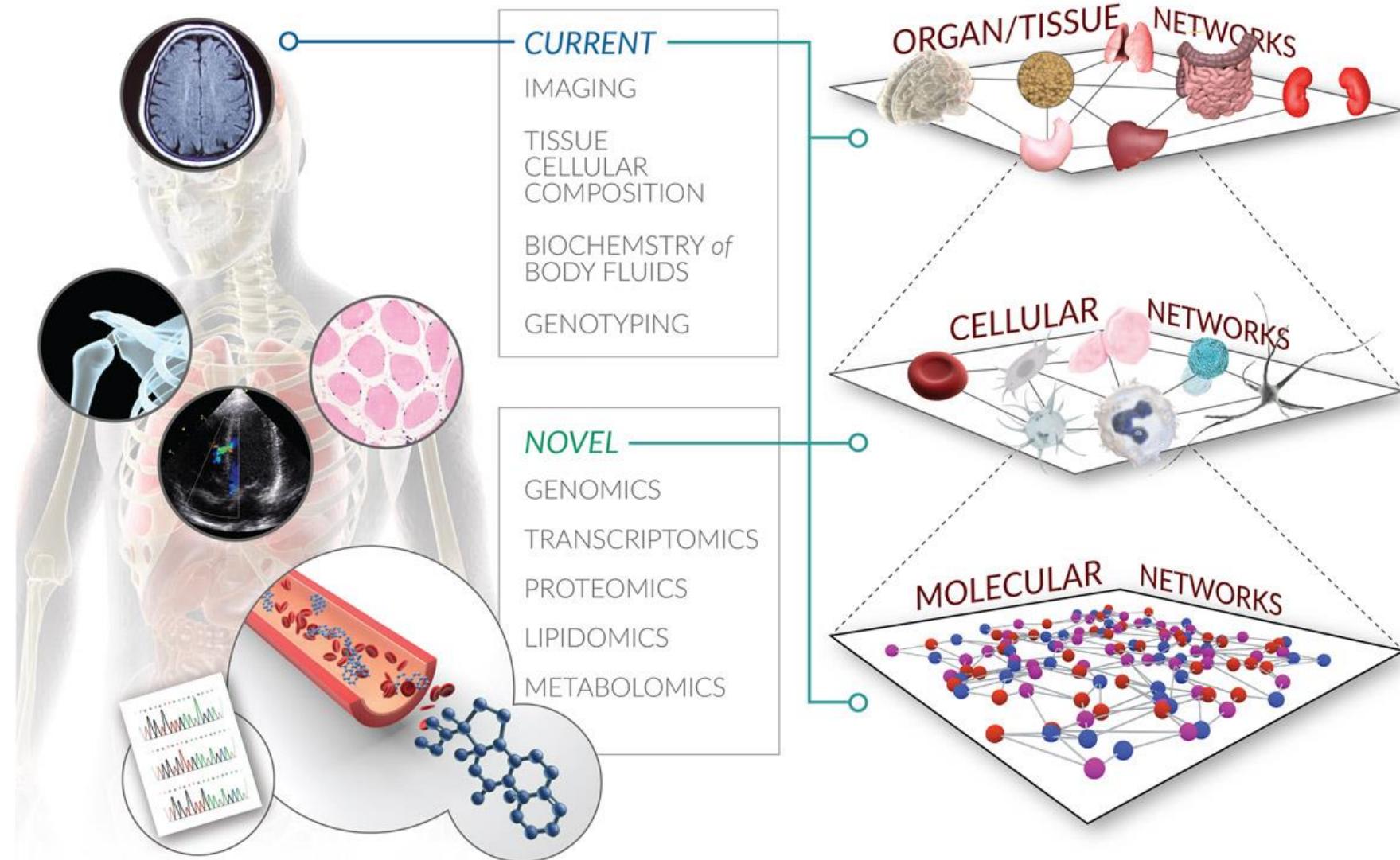


<https://doi.org/10.1016/j.neuroimage.2020.117046>



<https://www.humanbrainproject.eu/en/>

DIAGNOSTIC APPROACHES



Full scale integration

- Key goal of systems biology: construct networks at different cellular levels to investigate cellular machinery.
- Currently no satisfactory method to construct an integrated cellular network.

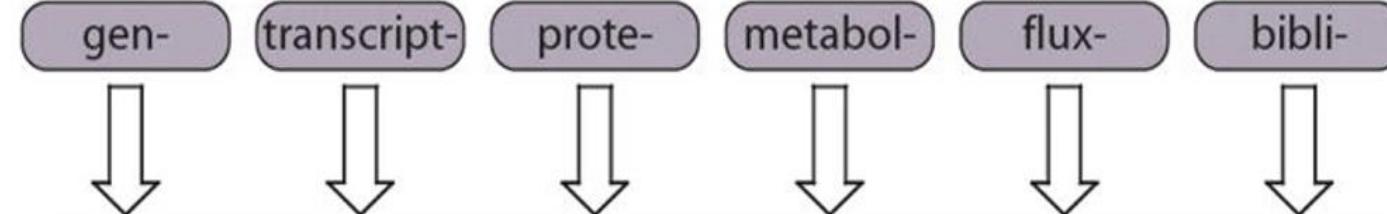
The challenge

- Interpret largescale data sets and extract true information to understand biological systems.
- Computational techniques, which can integrate and combine these large and heterogeneous data sets, will help gain more biological insights.

The Systems Biology paradigm:

Components -> networks -> computational models -> phenotypes

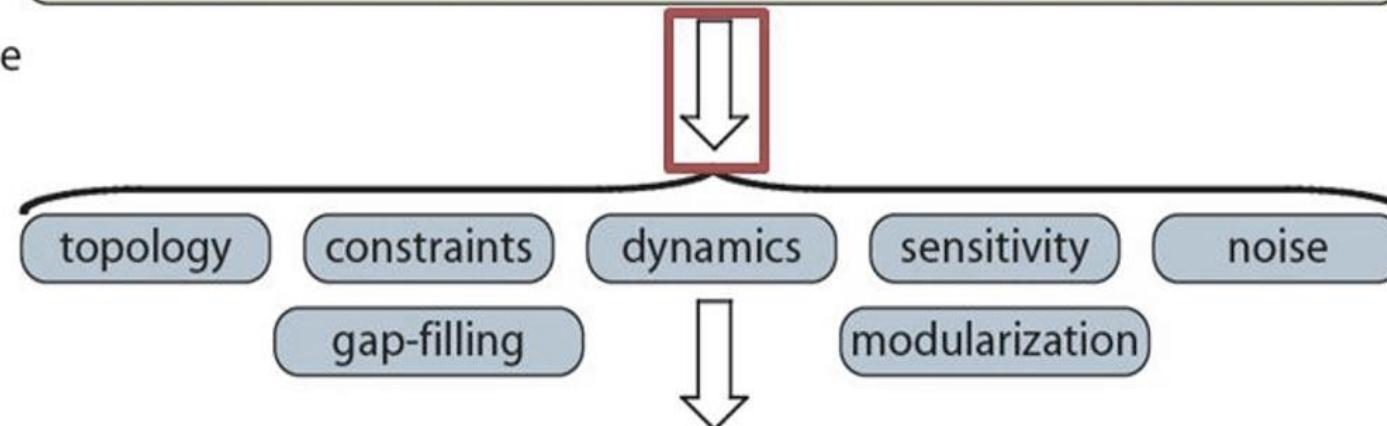
1. Database:
- Plurality of -omics



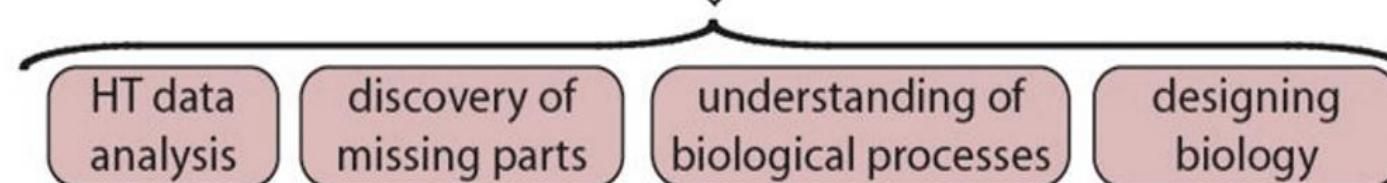
2. Knowledge Base:
- One set of reactions
encoded by a genome

reconstruction of biochemical reaction network

3. *In silico* modeling:
- Query Tools

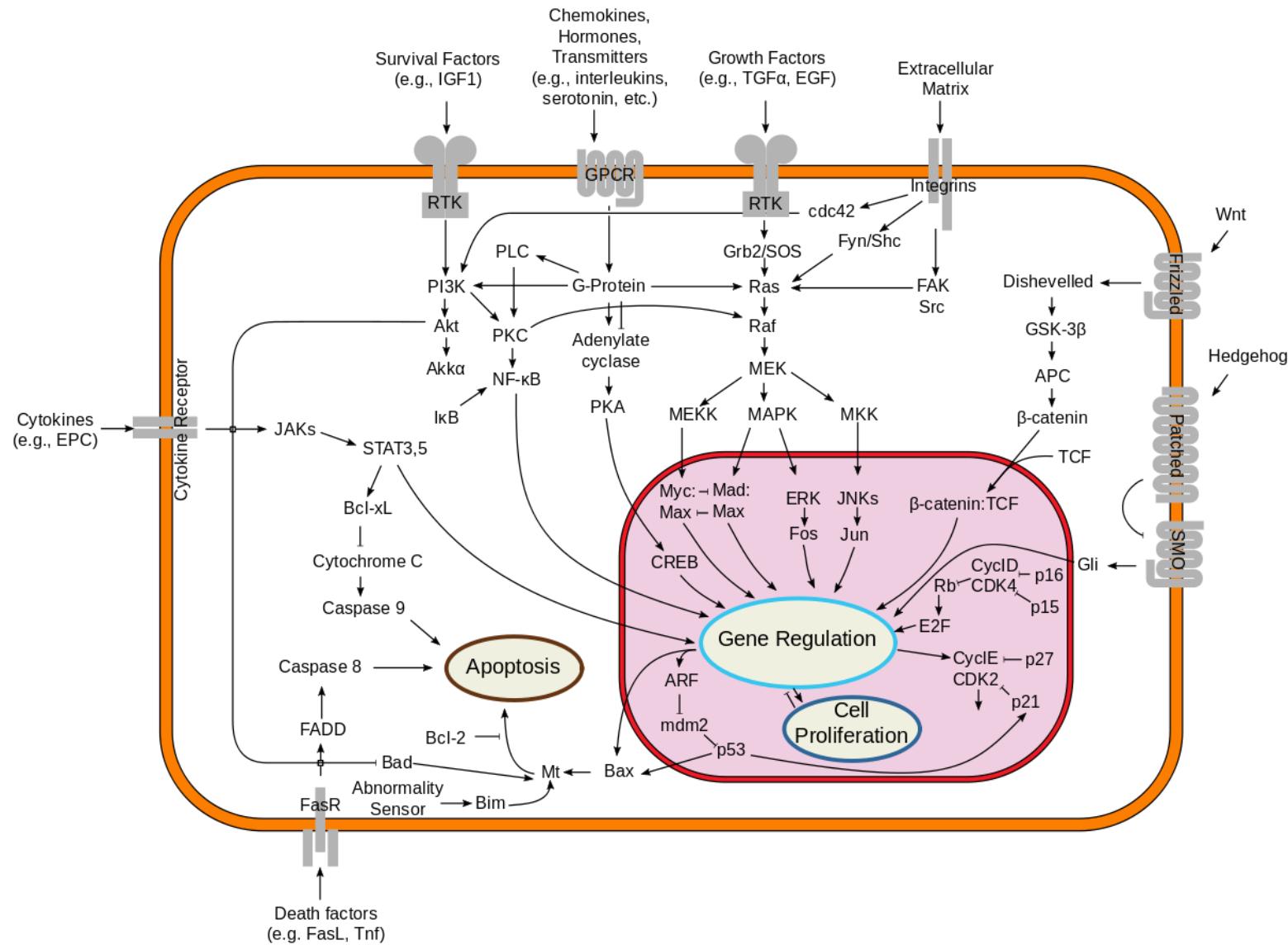


4. Validation, Discovery,
and Use



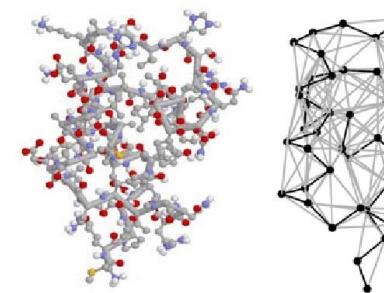
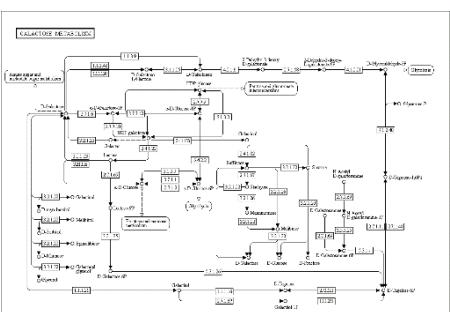
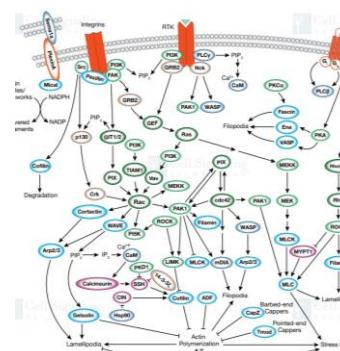
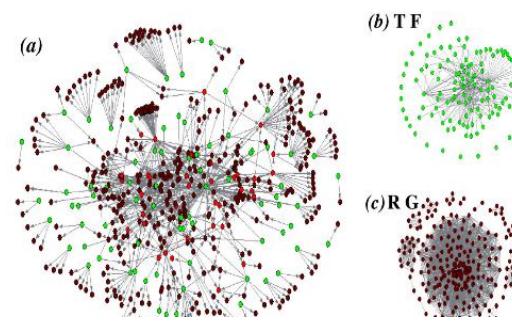
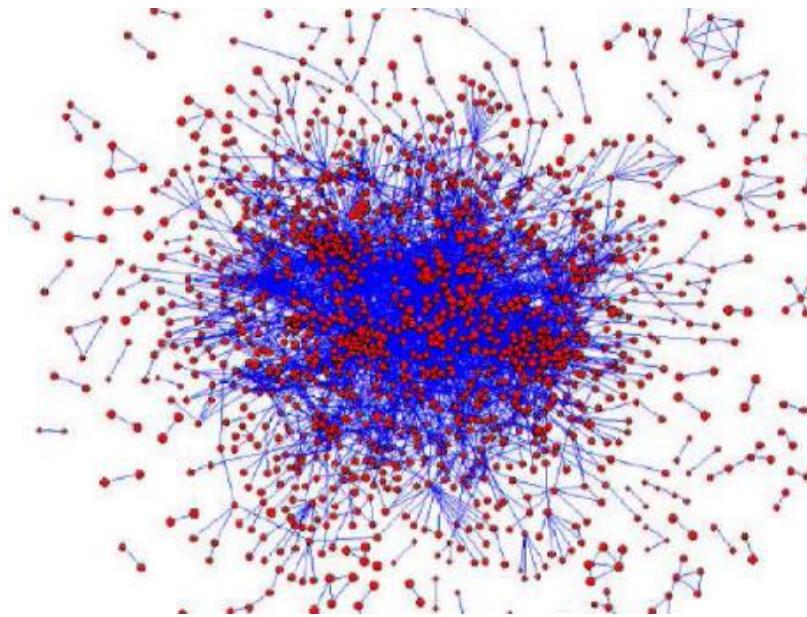
Viewing cells in terms of their underlying network

Organizing biological information in the context of networks is a powerful concept, networks can be seen as graphs.



Intra-cellular networks

- Transcriptional regulation networks
- Protein structure networks
- Metabolic networks
- Protein-protein interaction (PPI) networks
- Cell signaling networks



How do we construct a network?



- **Bottom up (from scratch)**
 - Literature based
 - Curation
 - Databases
 - Previous Knowledge
 - From local to global
- **Top down (data driven)**
 - Data dependent
 - Algorithms
 - Inference
 - Reverse engineering

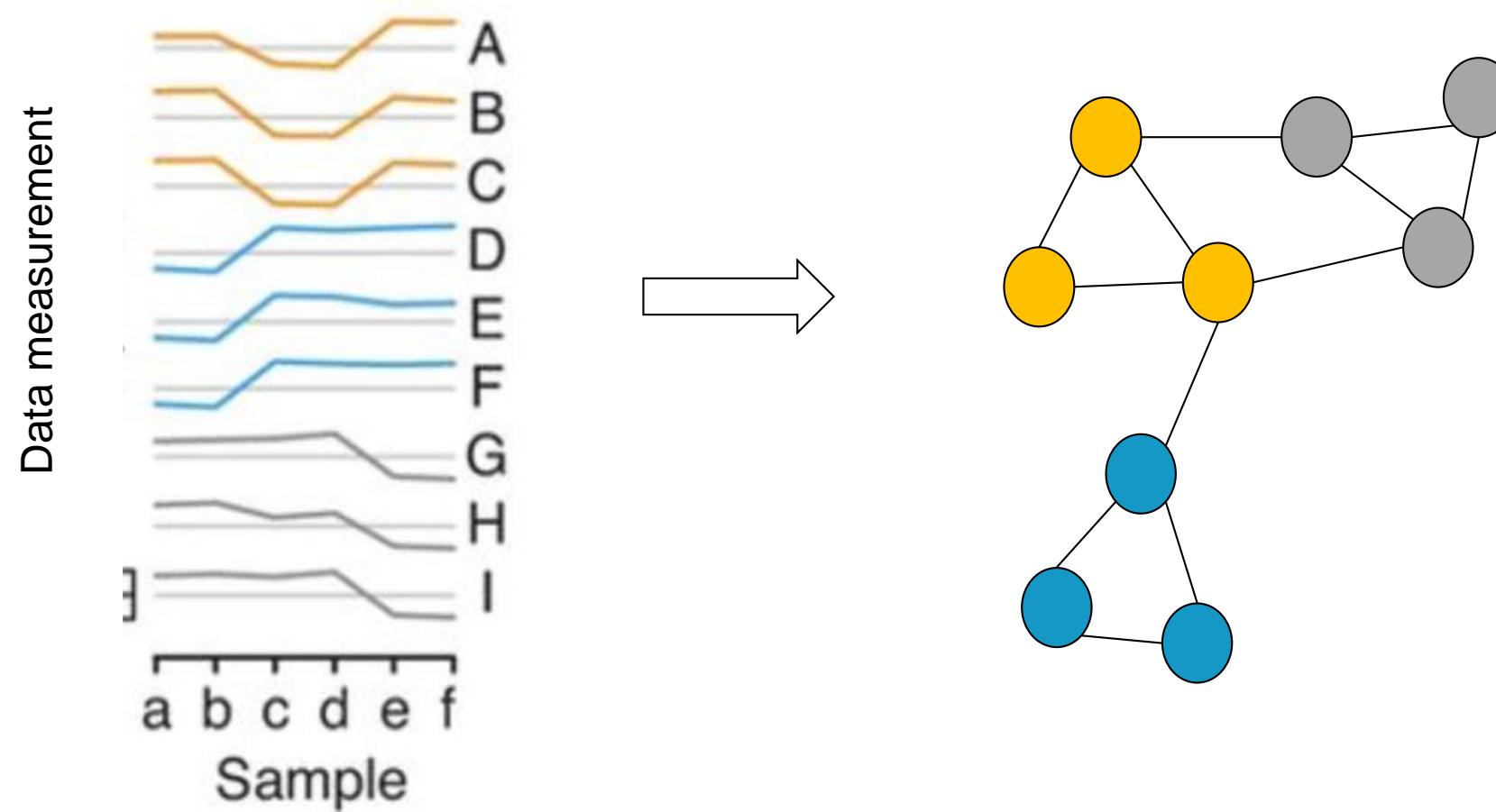
Can you name some problems and advantages for both approaches?



Top down
Data driven network inference

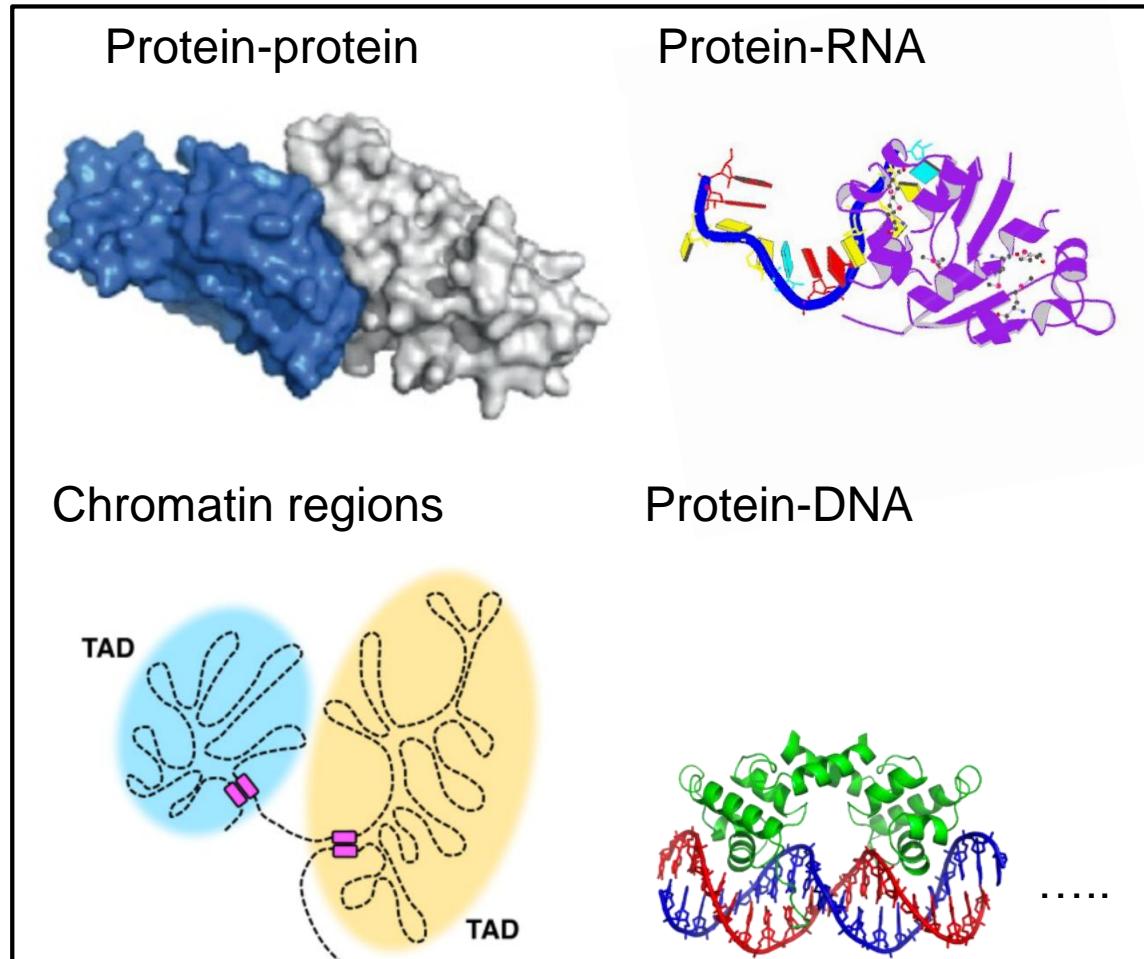
What is network inference?

"process of revealing the network structure of a biological system by reasoning backward from observed data."
He et al, 2009



Why do we need network inference?

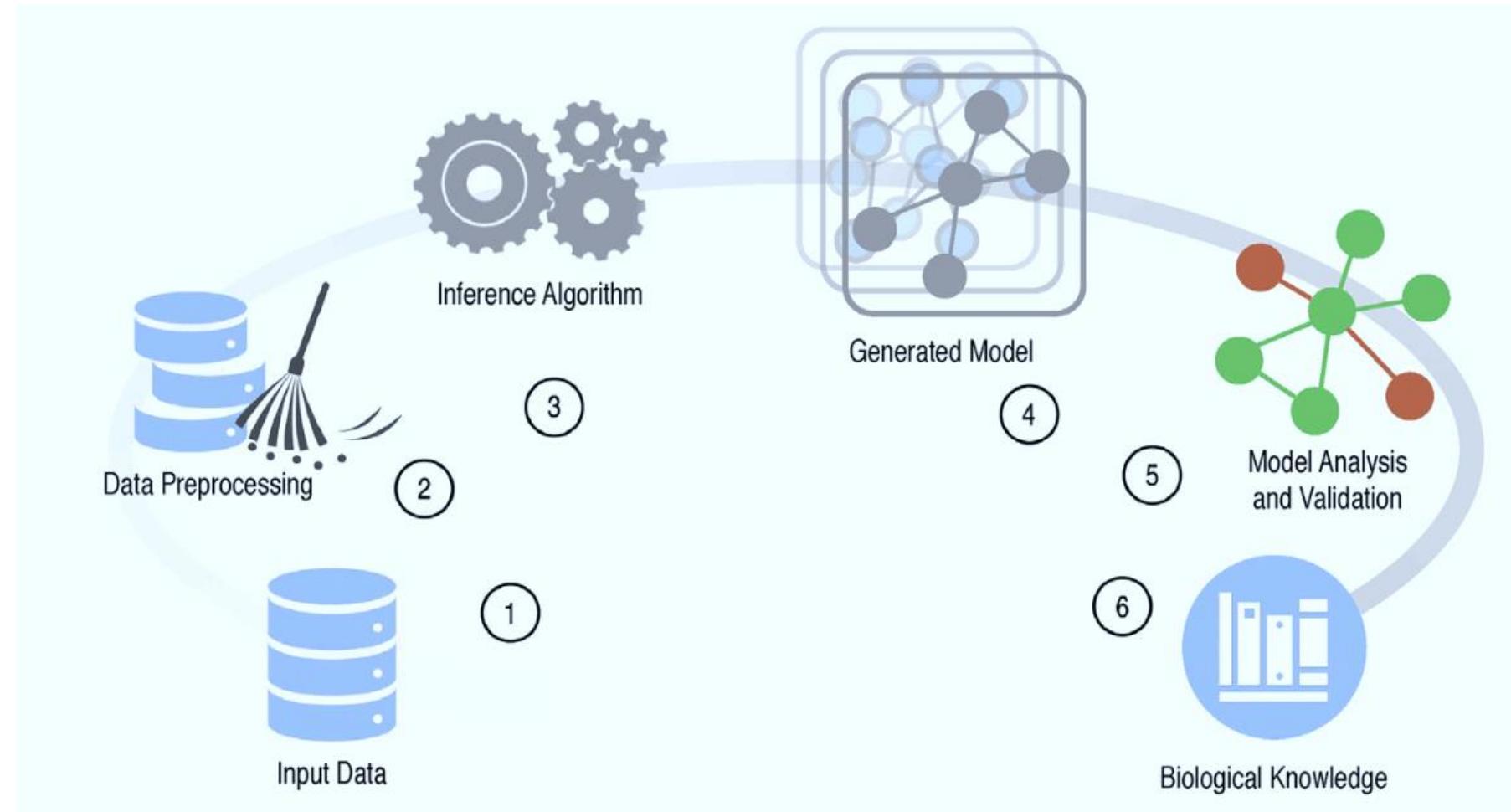
Most/All functions in cells are performed through interactions



Interactions are hard to measure

Abundances are easier to measure

Network inference process



Strengths/weaknesses of network inference types

Computational approach	Strengths	Weaknesses
Information-theory models	<ul style="list-style-type: none">• Large GRNs, even out of low expression genes• Mutual and conditional mutual information approach• Not computationally-demanding• Low number of samples	<ul style="list-style-type: none">• Regulation by multiple genes is not considered• Static, only suitable for steady-state data
Examples:	REVEAL [36], RELEVANCE [40,84], ARACNE [42], CLR [43], MRNET [44]	
Boolean models	<ul style="list-style-type: none">• Capable of inferring large networks• Generally easy to interpret• Simplify underlying complex biological phenomena• Allow supervised learning methods	<ul style="list-style-type: none">• Deterministic nature• Discretization bottleneck (only on/off states)• Problems in handling incomplete or inconsistent expression data• High computing time• Most of them use small number of genes
Examples:	RCGA [85], TRaCE + [86], CABeRNET [87]	
ODE models	<ul style="list-style-type: none">• Directed signed graphs• Realistic dynamics• Suitable for both steady-state and time series expression data• Simplification of the system by means of linear functions• Allow prediction of the behaviour of the network under different conditions once parameters are known	<ul style="list-style-type: none">• Not suitable for large networks• Linear functions also constrain the dynamic behaviour of cell regulatory functions (e.g. oscillations, multistationarity)• Hard to find appropriate values for model parameters• Noisy data leads to qualitative instead of quantitative GRN inference
Examples:	SCODE [68], HiDi [69]	
Bayesian models	<ul style="list-style-type: none">• Noise and uncertainty handling• Do not require a large number of involved variables• Integration of prior knowledge and allowance of enrichment analyses• Statistical inference of gene network	<ul style="list-style-type: none">• Feedback loops are not allowed• Fail in the inference using time series expression data• Cannot cope with large GRNs• Inherent combinatorial learning
Examples:	F-MAP [88], MDP [89], POMDP [71], QMR-DT [73]	
Neural models	<ul style="list-style-type: none">• Recognize an input pattern• Model any functional relationship inferable from the data• Suitable for both steady-state and time series expression profiles• Noise handling and biologically plausible• Manage non-linear and dynamic behaviour	<ul style="list-style-type: none">• Machine training experiments are hard to perform since every situation requires a different learning rate definition• Computational complexity makes them more suitable for very small systems
Examples:	ANN [27], RNN [78], ELM [83]	

Considerations when choosing approach

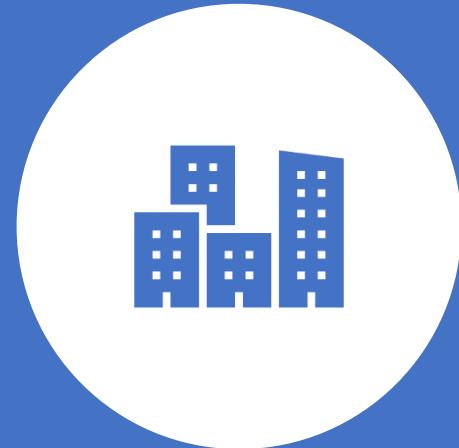
1. Simplicity/interpretability
2. Scalability
3. Assumptions (e.g. can we assume linear relationship?)
4. Sensitivity vs specificity
5. Ability to model feedback loops and combinatorial regulations
6. Availability of data: how much, statistical independency, data points, etc
7. Pitfalls of different network types: e.g. from mRNA to gene regulatory networks:
mRNA abundance is a proxy for activity and presence of regulators, not a direct influence
8. Integrating prior knowledge improves results

Considerations for experimental design / input data

- Network inference is a largely undetermined problem. i.e. has multiple solutions
- To help deconvolute uncertainties, the best experimental design includes
 - Perturbation data
 - Steady-state (more realistic as cheaper) or time course (ideal)
 - Timing for measurements is important
- Bigger scale of network to infer requires more data
- Replicates are needed to remove stochastic error and ensure quality of data

Optimization of networks

- Dimensionality reduction can help focus on ‘interesting’ features/genes
 - E.g. Feature selection: remove genes with low expression or no changes
- Structure/topology optimization against experimental datasets
 - Forward selection (growing network and evaluating)
 - Backward elimination (pruning and evaluating)
- Integration of prior knowledge has been shown to almost always increase accuracy
- Integration of other datasets also has been promising but tools are in early development stage



Bottom up
network construction

		Metabolic	Protein-protein	Regulatory/ Signaling	Organisms	Curation ^a
KEGG	http://www.genome.jp/kegg/	x			many	C
BiGG	http://bigg.ucsd.edu/	x			many	M
BioCyc ^b	http://biocyc.org/	x		x	many	C/M
MetaCyc	http://metacyc.org/	x			many	C/M
Reactome	http://reactome.org/	x	x	x	many	M
BIND	http://www.bindingdb.org/		x		many	E/M
DIP	http://dip.doe-mbi.ucla.edu/		x		many	M
HPRD	http://www.hprd.org/		x		human	M
MINT	http://mint.bio.uniroma2.it/		x		many	M
Biogrid	http://www.thebiogrid.org/		x		many	E
UniHI	http://theoderich.fb3.mdc-berlin.de:8080/unihi/		x		human	E/M
YeastRACT	http://www.yeastract.com/			x	yeast	M
TRANSFAC	http://www.gene-regulation.com			x	many	M
TRANSPATH	http://www.gene-regulation.com			x	many	M
RegulonDB	http://regulondb.ccg.unam.mx/			x	many	C/E
NetPath	http://www.netpath.org/			x	human	M

^aM=Manual/Literature, C= Computational, E= Experimental.

^blinks to other *Cyc databases

Many sources available

	CBN	KEGG	Reactome	BioCarta	Wiki-pathways	SPIKE	UCSD signaling gateway	NCI pathway interaction database	NetPath
Species [human (Hs); mouse (Mm); rat (Rn)]	Hs, Mm*, Rn*	>20 species	Hs (curated) +20 species (inferred)	Hs, Mm	>25 species	Hs	Hs, Mm	Hs	Hs
Literature support displayed						✓	✓	✓	✓
At edge level	✓								
At pathway level		✓	✓	✓	✓			✓	✓
Defined biological boundaries									
Species	✓	✓		✓	✓	✓		✓	✓
Tissue	✓								
Disease context	✓	✓			✓				✓
Biological pathways	✓	✓	✓	✓	✓	✓		✓	✓
Manual curation	✓	✓	✓	✓	✓	✓	✓	✓	✓
Data-driven enhancement	✓						✓		✓
Crowd curation	✓			✓	✓				±
Directional edges	✓	✓	✓	✓	✓	✓	✓	✓	✓
Multiple types of entities	✓	✓	✓	✓	✓	✓	✓	✓	✓
Interactive visualization	✓		✓		✓				
Computable	✓	✓	✓						
Available for download	✓	✓	✓		✓	✓	✓	✓	✓
Size	>120 network models	>450 pathway maps	>1400 pathways (Hs)	>350 pathways	>430 pathways	>25 curated pathways	~3500 proteins and their proximal connections	>135 NCI-Nature curated pathways (+Reactome + BioCarta)	>30 curated pathways (immune signaling/cancer)

*coming soon

Causal biological network database: a comprehensive platform of causal biological network models focused on the pulmonary and vascular systems

**IMEx**

The International Molecular Exchange Consortium

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- MBInfo (Active)
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- MatrixDB (Active)
- Molecular Connections (Active)
- I2D (Active)
- InnateDB (Active)
- UCL-BHF group, UCL London (Active)
- UniProt group (Active)
- Swiss-Prot group, SIB (Active)
- EMBL-EBI (Active)
- BioGRID (Observer)
- PrimesDB (Observer)
- MPact (I)
- BIND (In)
- MPIDB (

IMEx data

- A non-redundant set of physical molecular interaction data from a broad taxonomic range of organisms.
- Expertly curated from direct submissions, peer-reviewed journals or pre-prints to a consistent high standard.
- Available in standard formats [MITAB](#) or [PSI-MI XML 2.5](#).
- Provided by a network of participating major public domain databases.

Available Interaction Network Data

<http://www.imexconsortium.org/about/>

Integrated Data Sources

Open Source

- Pathway Commons
- BioGRID
- MiMI (Michigan Molecular Interactions)
- STRING (Search Tool for Retrieval of Interacting Genes/Proteins)
- Genes2Network
- VisANT (Integrative Visual Analysis Tool)
- BIOBASE

Proprietary

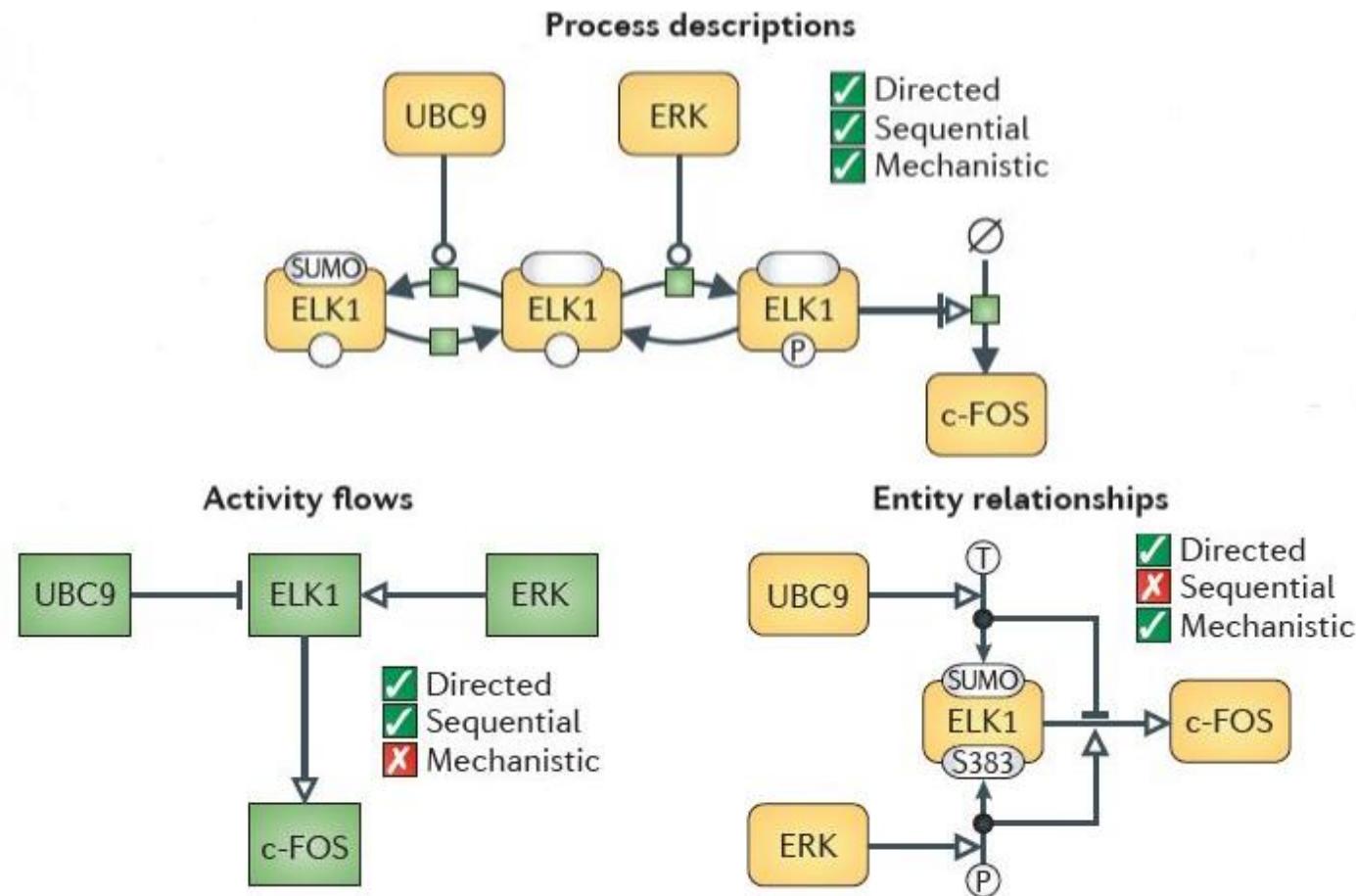
- IPA (Ingenuity Pathway Analysis)
- MetaCore

USING FORMALIZED DIAGRAMS TO REPRESENT Biological Networks



Systems Biology Graphical Notation (SBGN)

Describing mechanisms in a systematic fashion

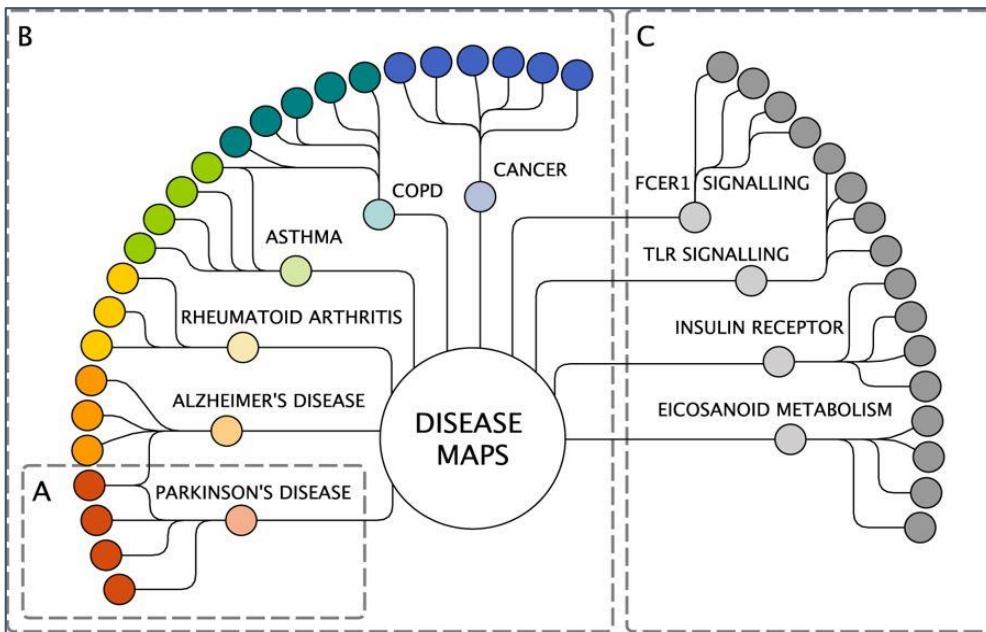


Process description diagrams of biological mechanisms

- Pioneering works of Prof. Hiroaki Kitano.
- Process description representation of signalling networks.
- First comprehensive disease-relevant extensive reconstructions of signalling pathways.
- Cancer Signalling Atlas – Curie Institute -
<https://acsn.curie.fr/ACSN2/ACSN2.html>
- Disease Maps project <https://disease-maps.org/>
- REACTOME – PD like diagrams <https://reactome.org/>

The Disease Maps project

Large-scale open community effort



Key goals

Create

formalized mechanistic networks at different levels to investigate cellular machinery and host pathogen interactions.

Interpret

large-scale data sets and extract true information to understand how the disease takes place and progresses.

Develop

computational techniques, which can integrate large and heterogeneous data sets and combine them with prior knowledge.

Build

computational models that can provide insights into the mechanisms of interest.

Molecular interaction maps



Representations of biological processes (disease mechanisms) that are both human and machine-readable.



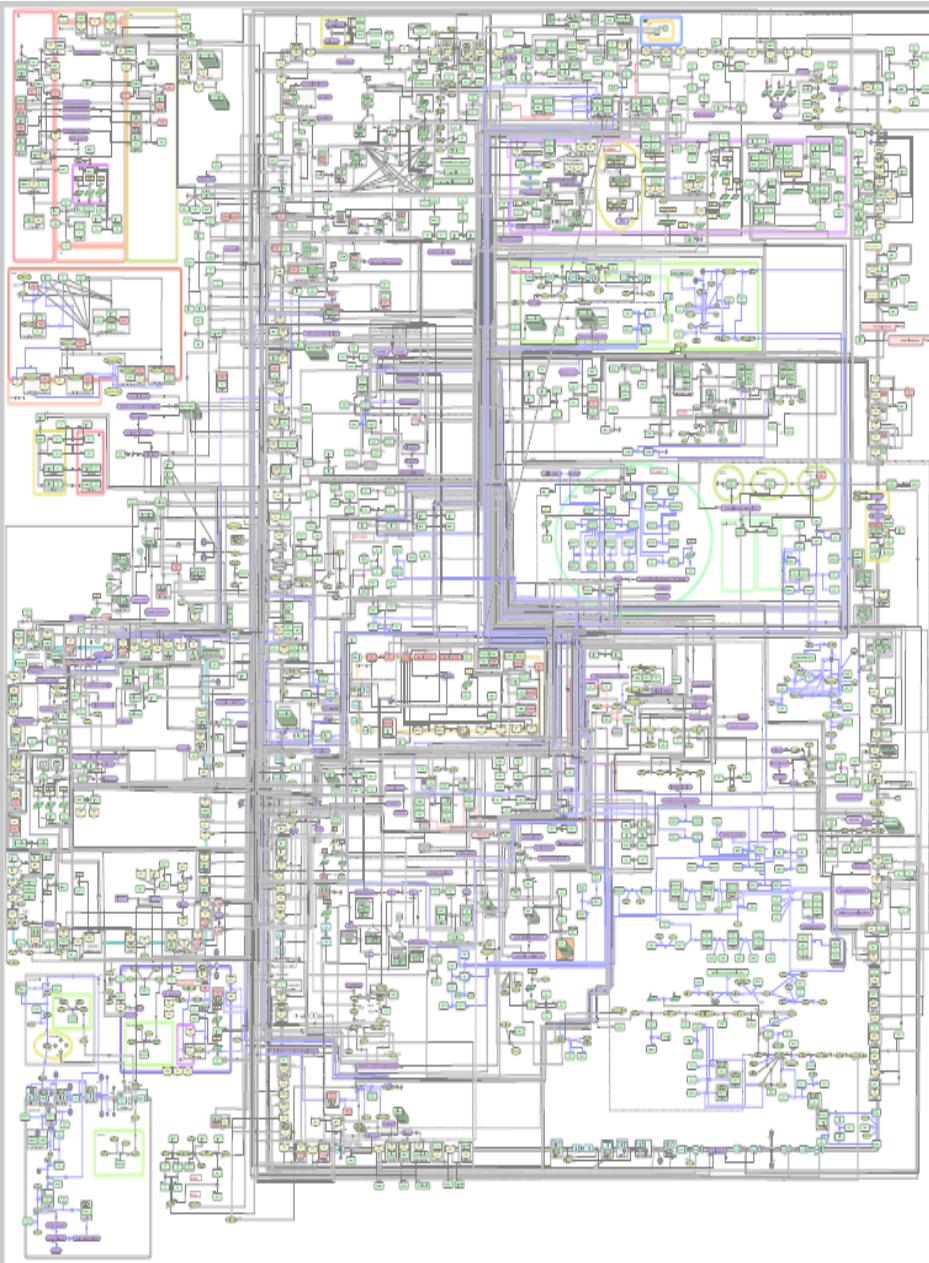
High quality source of knowledge (signalling pathways, gene expression, cellular phenotypes)—template for data visualization.



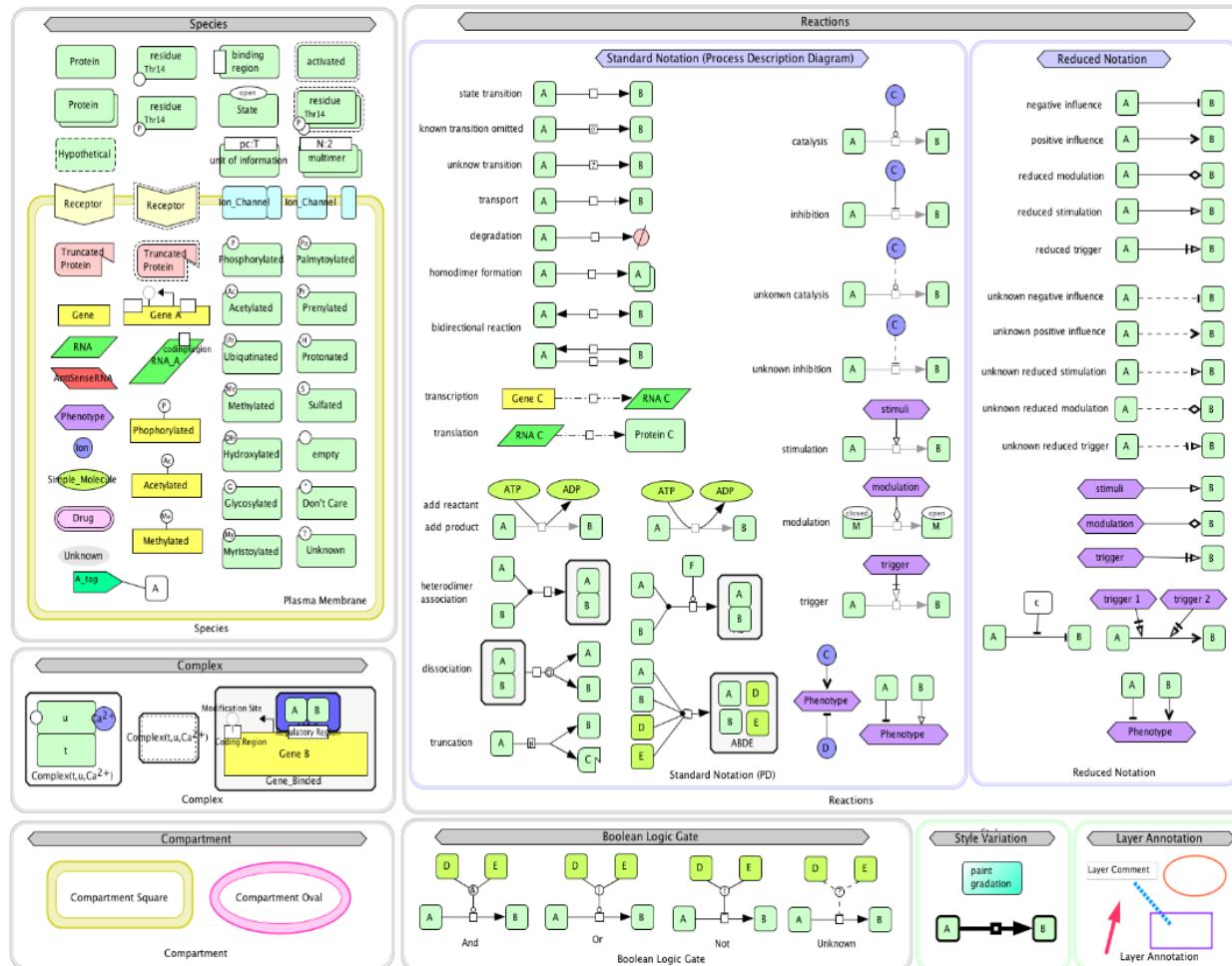
Can be seen and analyzed as **a complex network** (topology/structure).



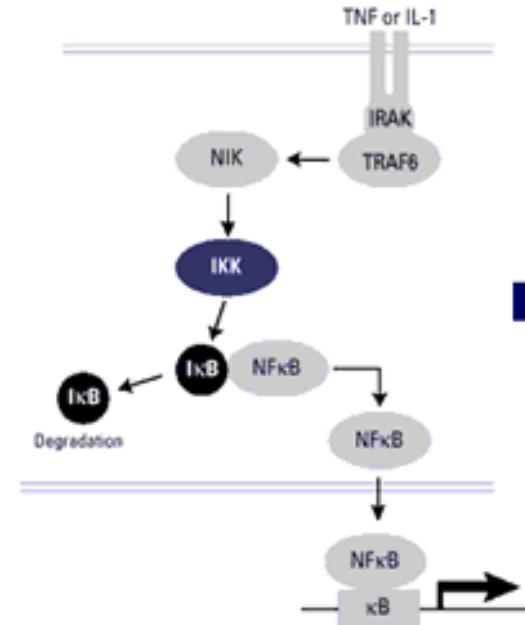
Can serve as a scaffold for a **mathematical model**.



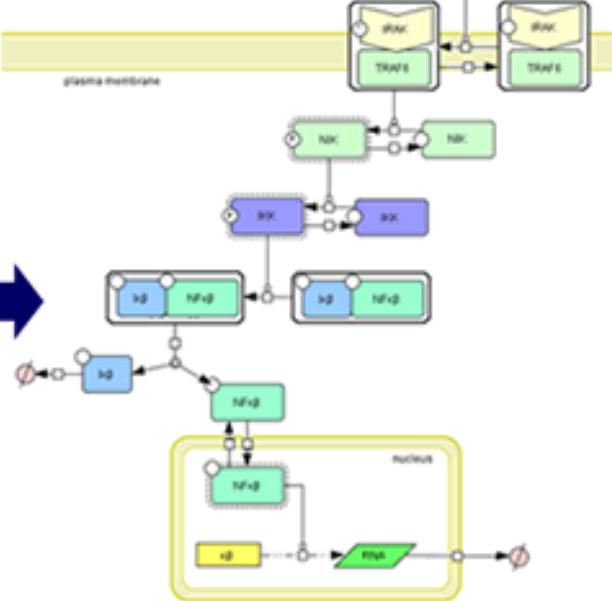
Building molecular maps using CellDesigner



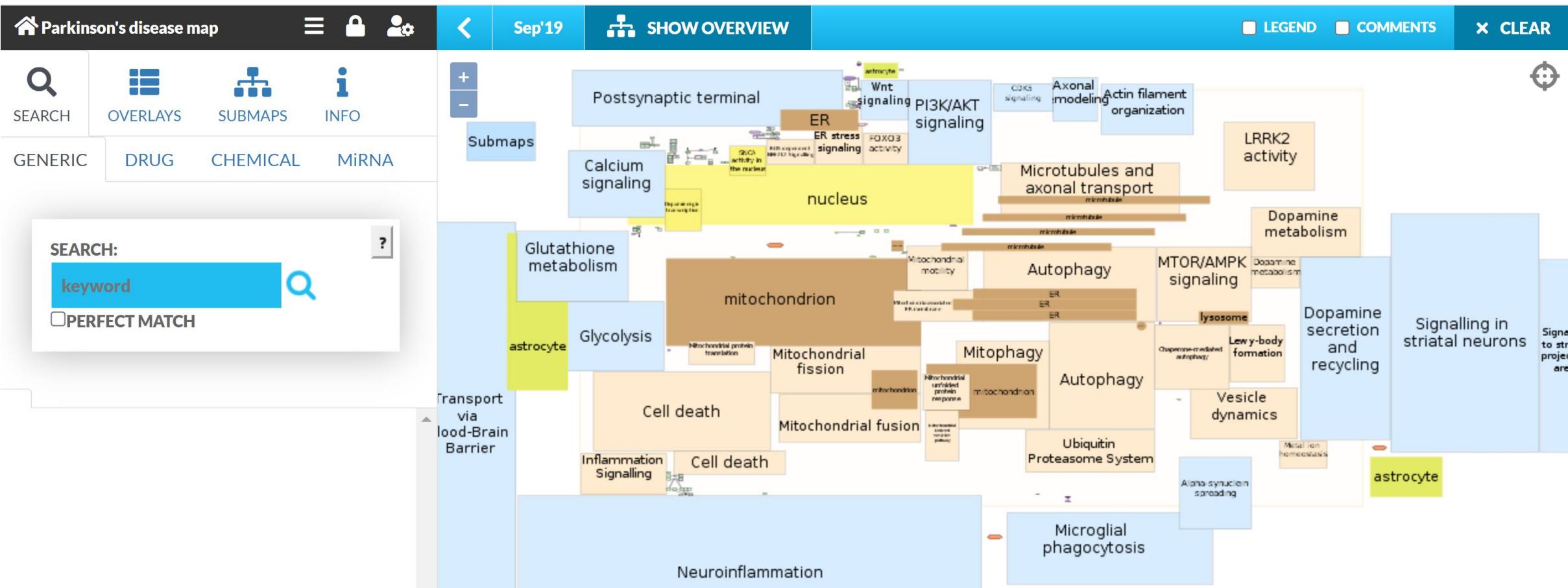
NF κ B Pathway



conventional diagram



CellDesigner's diagram

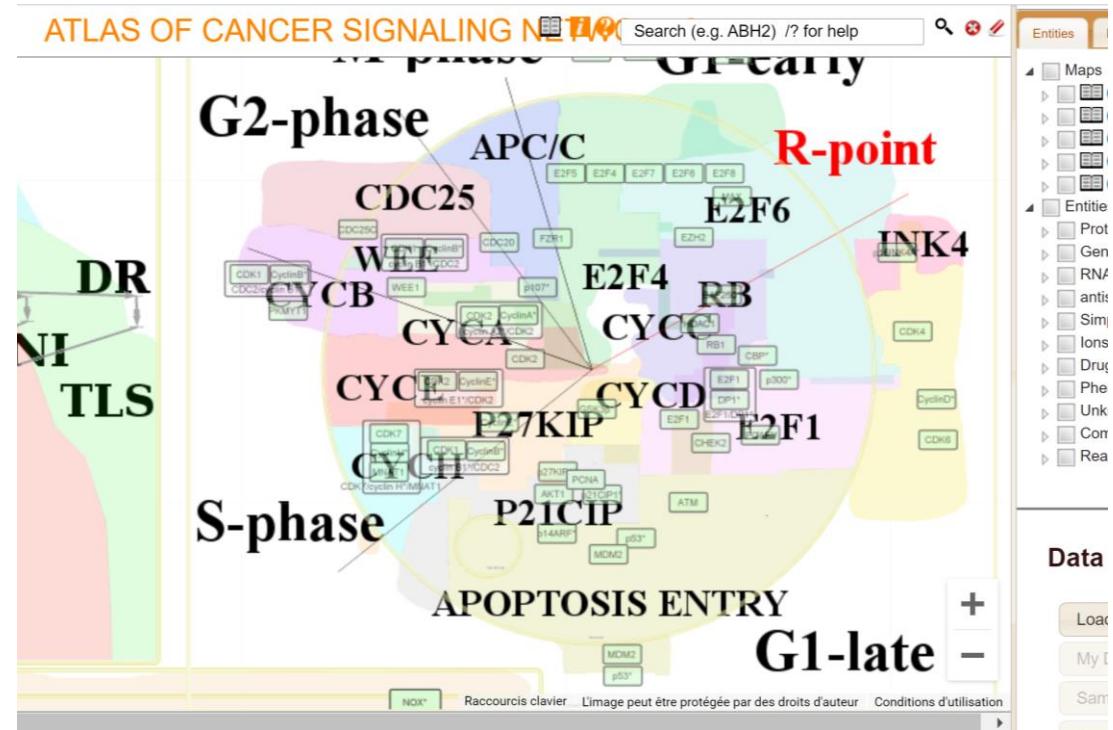
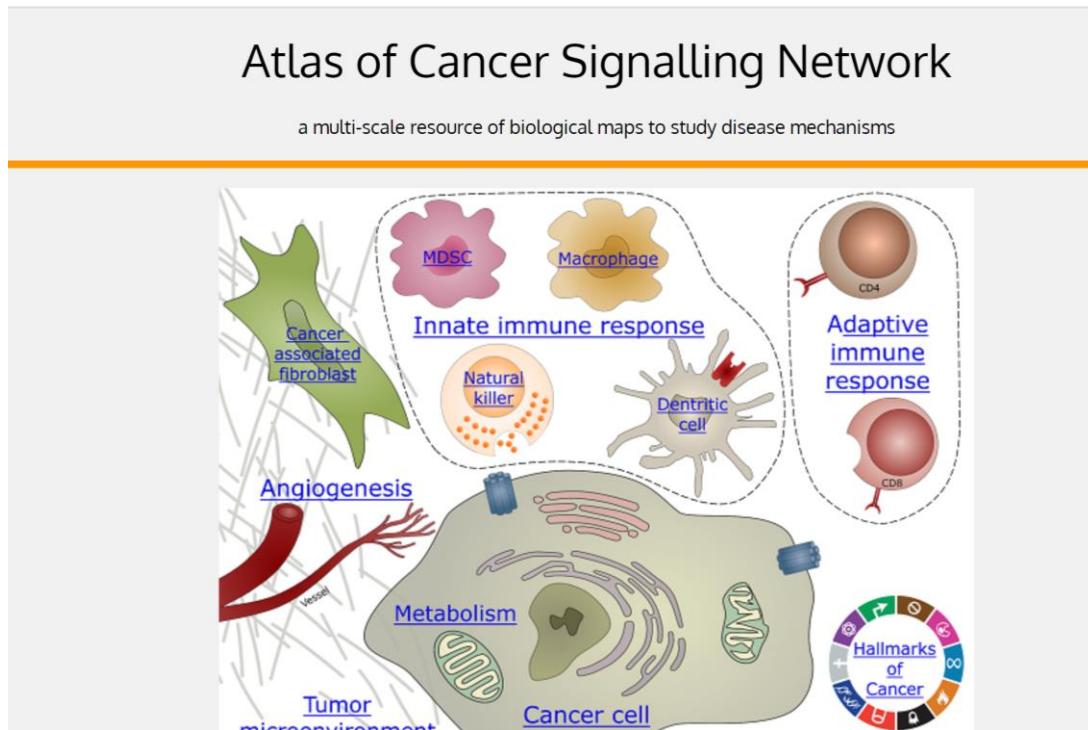


The Parkinson's map
<https://pdmap.uni.lu/Minerva/>

- Minerva platform
- Large scale curation effort
- Interdisciplinarity
- PD and AF

Atlas of Cancer Signalling Network

<https://acsn.curie.fr/navicell/maps/acsn/master/index.html>

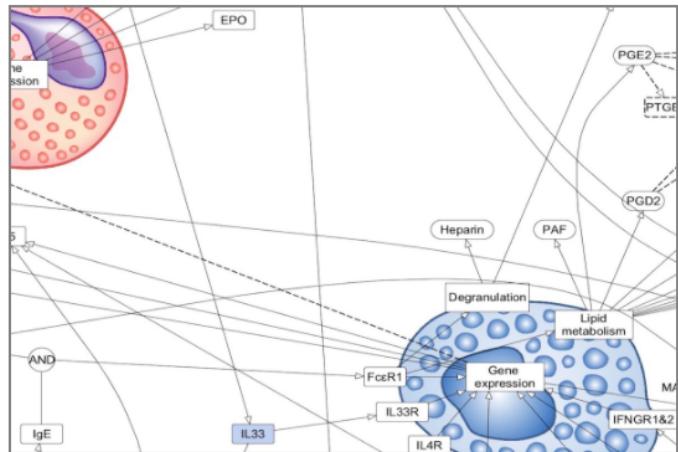


- Large collection of cancer associated pathways
 - Navicell
 - Large scale effort
 - PD and AF

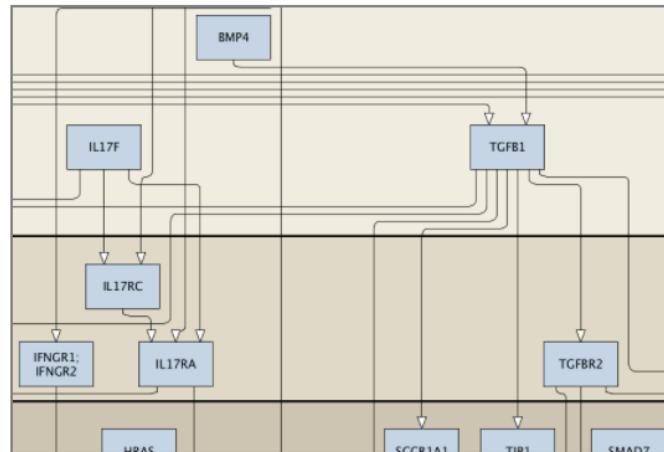
AsthmaMap architecture

The AsthmaMap includes three interconnected layers of granularity: Cellular Interactions (CI), a high-level overview; Molecular Relations (MR), the intermediate level of details; Biochemical Mechanisms (BM), the most detailed layer.

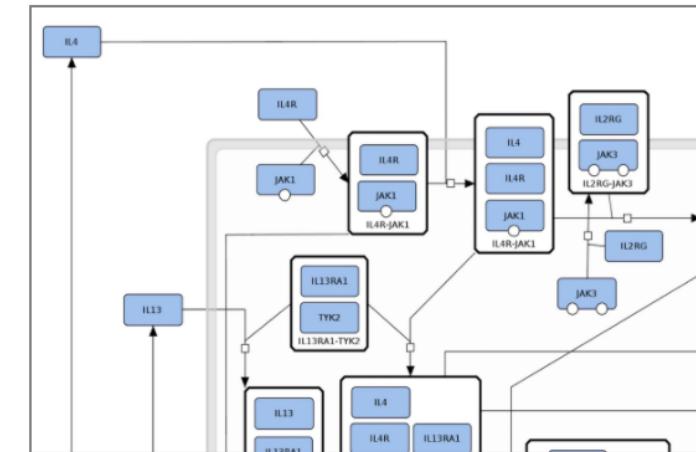
AsthmaMap Cellular Interactions



AsthmaMap Molecular Relations



AsthmaMap Biochemical Mechanisms



The Asthma Map

<https://asthma-map.org/>

- Granularity
- Different layers
- PD
- AF

The RA map

<https://ramap.uni.lu/minerva/>

- SBGN compliant, fully PD
- Detailed annotations using MIRIAM identifiers
- Executable through a map-to-model framework (PD→AF)

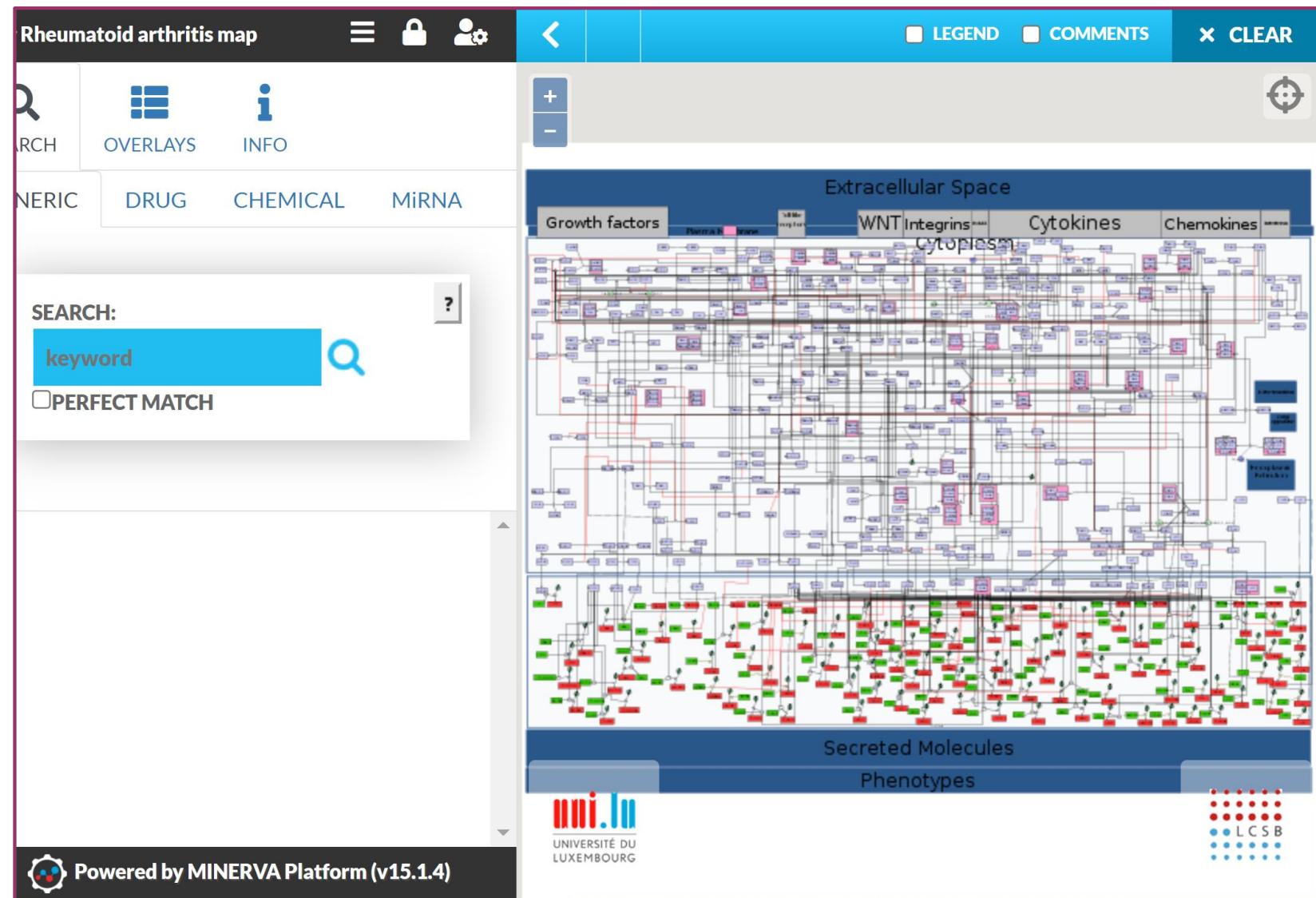
JOURNAL ARTICLE

RA-map: building a state-of-the-art interactive knowledge base for rheumatoid arthritis 

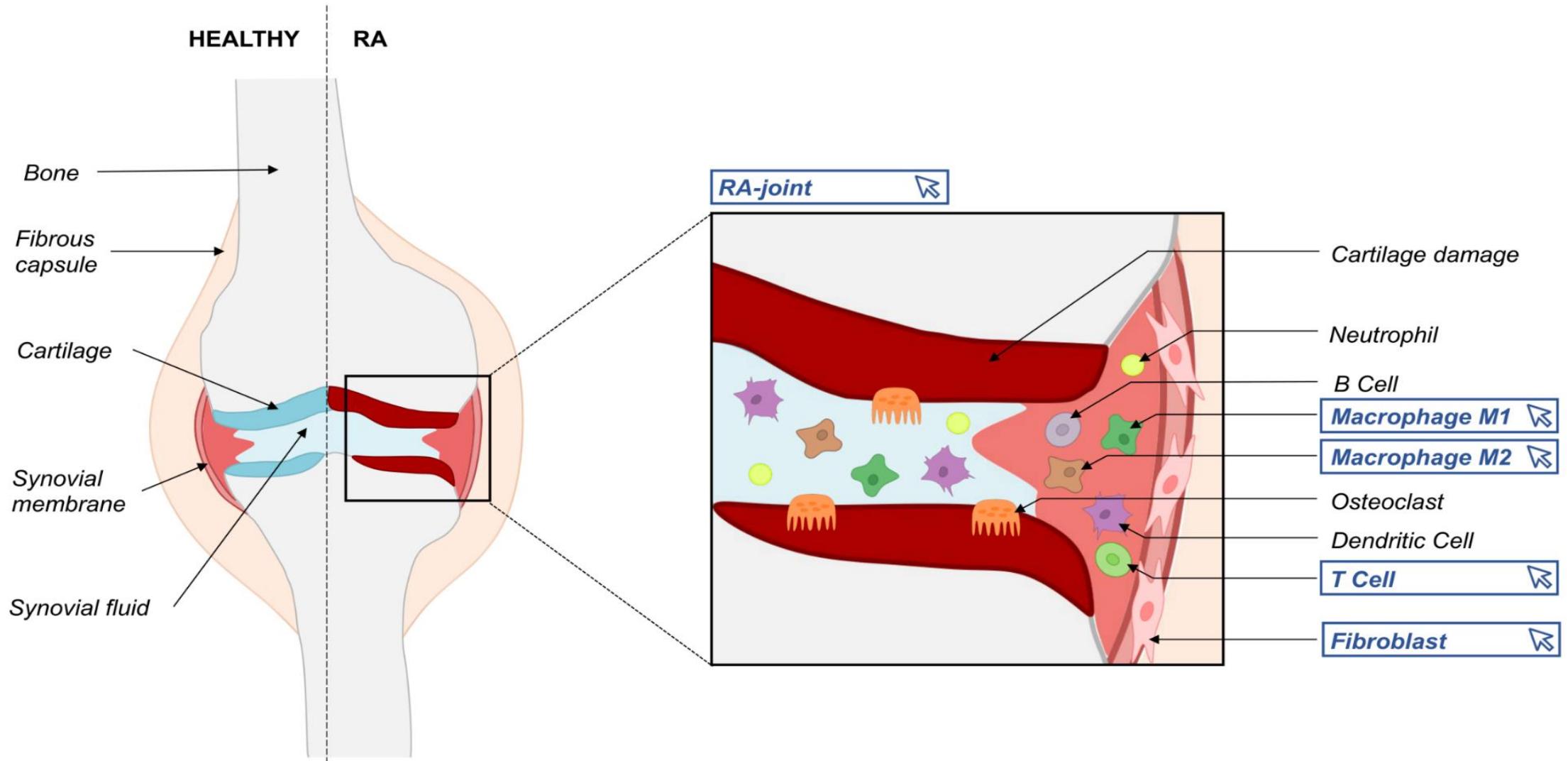
Vidisha Singh, George D Kalliolias, Marek Ostaszewski, Maëva Veyssiére, Eleftherios Pilalidis, Piotr Gawron, Alexander Mazein, Eric Bonnet, Elisabeth Petit-Teixeira, Anna Niarakis 

Database, Volume 2020, 2020, baaa017, <https://doi.org/10.1093/database/baaa017>

Published: 20 April 2020 Article history ▾

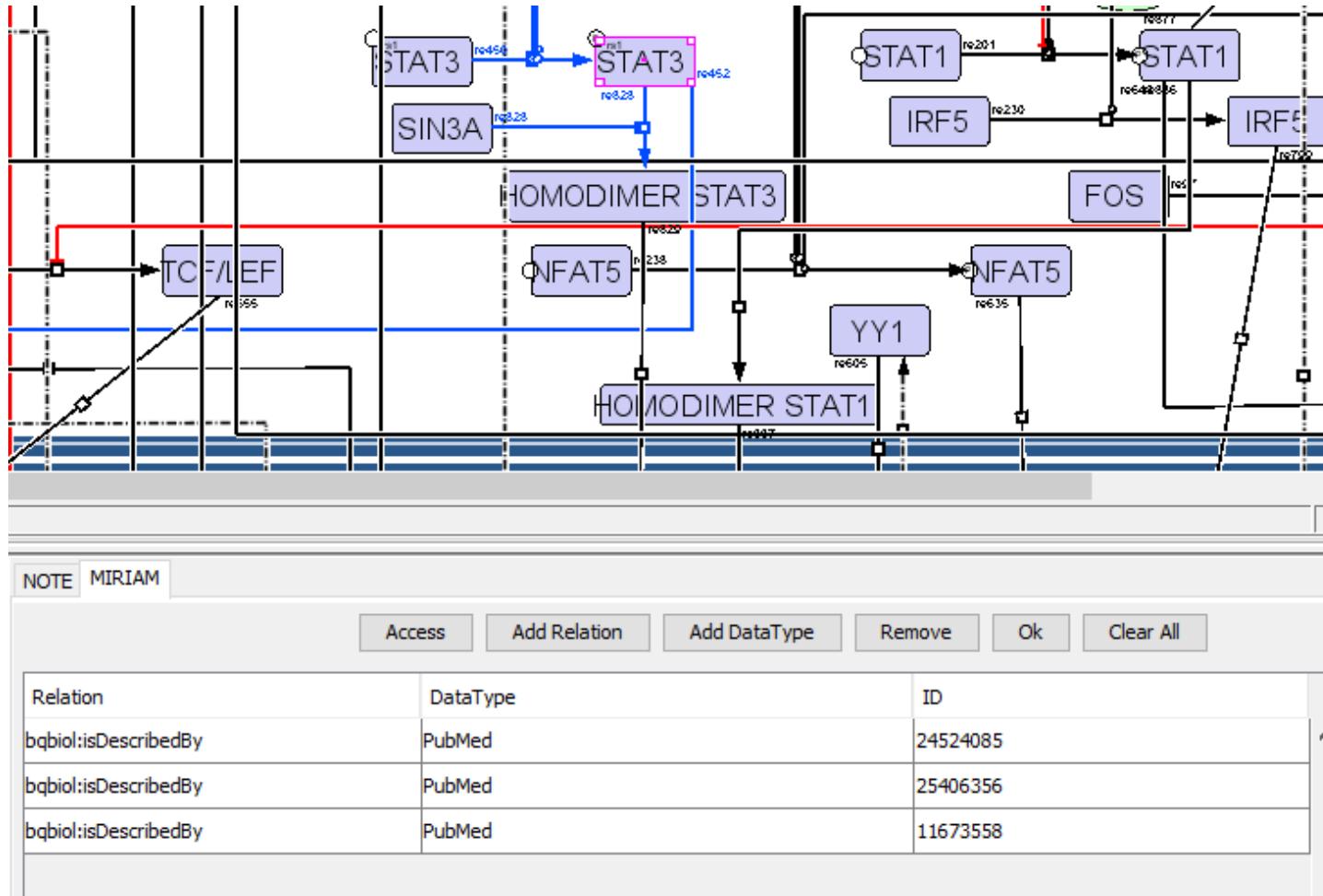


The RA –Atlas



Building molecular maps using CellDesigner

MIRIAM: Minimal Information Required In the Annotation of Models



- Facilitating interoperability and model reusability
- Annotations retrieved in the resulting model

Interactive knowledge base for RA using MINERVA –(Molecular Interaction NEtwoRk VisuAlization) platform



SEARCH OVERLAYS INFO

GENERIC DRUG CHEMICAL MIRNA

SEARCH: IL6 PERFECT MATCH

il6

1 RNA: IL6

Compartment: Nucleus
Full name: interleukin 6
Symbol: IL6
Former symbols: IFNB2
Synonyms: BSF2, HGF, HSF, IL-6
Annotations:
Source: Annotated by curator
[1] [PUBMED\(10688908\)](#)
[2] [PUBMED\(17652167\)](#)
[3] [PUBMED\(2462501\)](#)
[4] [PUBMED\(18281366\)](#)
[5] [PUBMED\(18454843\)](#)
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[7] [PUBMED\(22870451\)](#)
[8] [PUBMED\(8484679\)](#)
[9] [PUBMED\(12905466\)](#)
[10] [PUBMED\(28494214\)](#)
[11] [PUBMED\(18205922\)](#)

Extracellular Space

Growth factors, Plasma Membrane, Toll-like receptors, WNT, Integrins, RANKL, Cytokines, Chemokines, Interferon

Cytoskeleton

Mitochondrion, Endoplasmic Reticulum

Protein: IL6

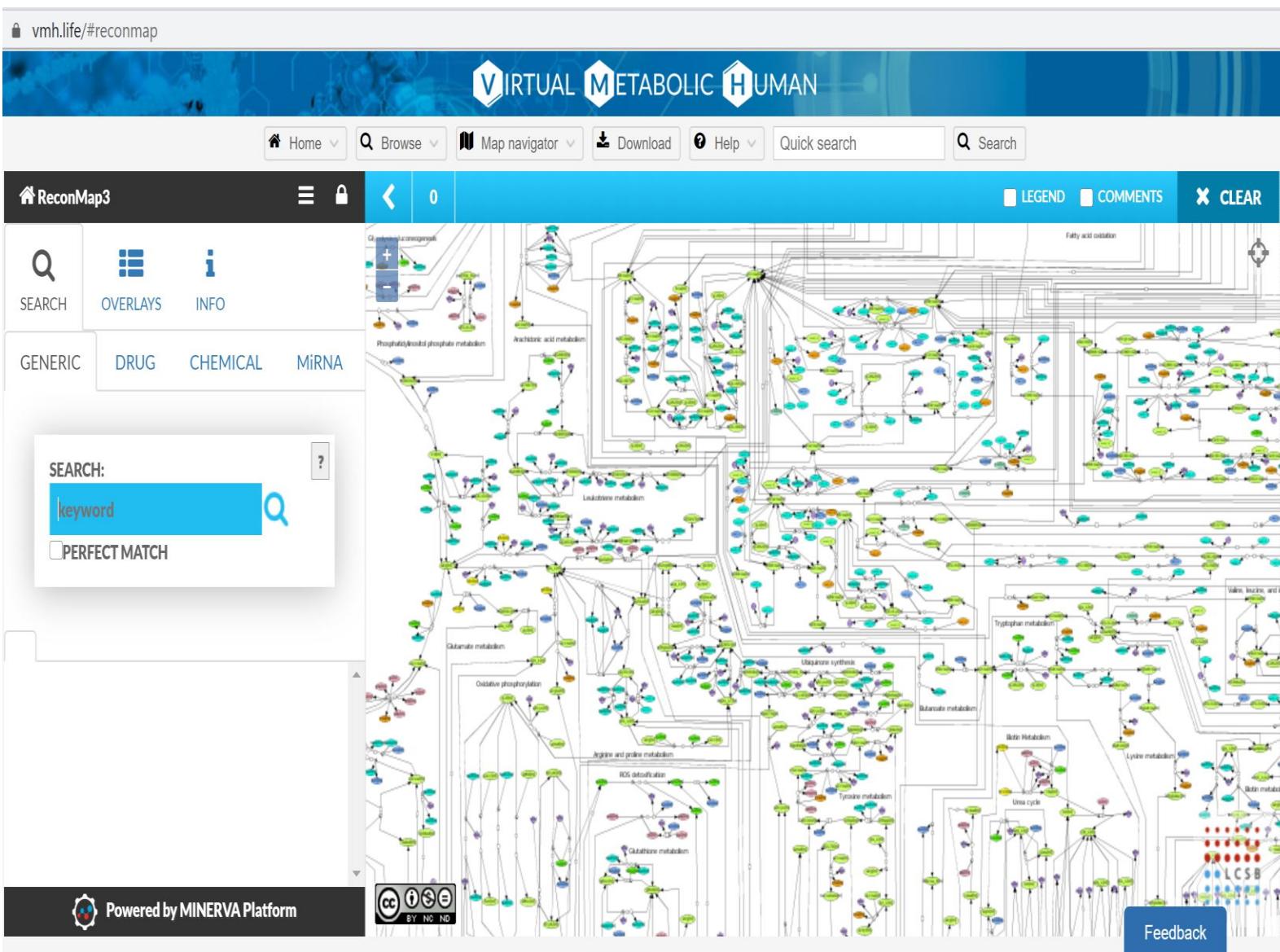
Interacting drugs

Interacting chemicals

Interacting Micro RNAs

The ReconMap

- ReconMap content obtained from the Virtual Metabolic Human database (VMH, <http://vmh.uni.lu>).
- Recon-derived simulation results can be visualized on ReconMap using a new extension to the COBRA Toolbox (Schellenberger et al., 2011).
- User can perform a simulation, e.g. Flux Balance Analysis, using the COBRA toolbox function ‘optimizeCBmodel’, then call the function ‘buildFluxDistLayout’ to write the input file for a context-specific ReconMap Overlay.





CellDesigner™: A modeling tool of biochemical networks



Current Release Version: CellDesigner 4.4.2

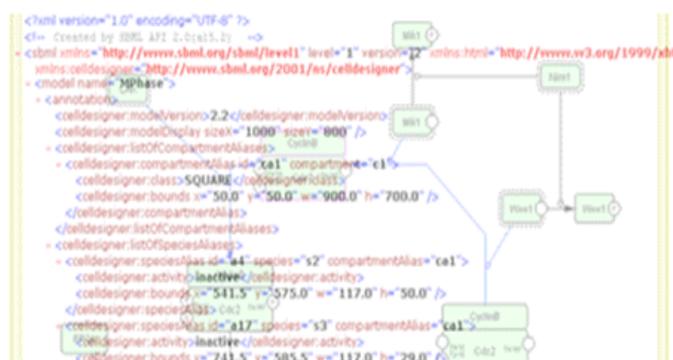
macOS Catalina and Ubuntu 18.04 support + Plugin APIs enhances + BioModels new API support + Garuda enabled + bug fixes. find out more...

You do not have to install JVM separately as it is included in the installer.

Check also:

- [CellDesigner on Garuda platform](#) (Ver4.4.1 Win / Mac)
- [Plugins / Utilities](#)
 - [CellDesigner Plugin API Document](#) (ver4.4.1)
- [Models built with CellDesigner](#)
- [BioModels.net models simulation results with CellDesigner 4.0](#)

What is CellDesigner™



Headlines

[CellDesigner 4.4.2](#) Mac installer updated for Catalina Support (2020/3/30)

[CellDesigner 4.4.2](#) is now available (2019/05/20)

[CellDesigner on Garuda platform](#) (2017/2/14) Garuda enabled Ver4.4 is available as Ver4.4.1 Win / Mac.

[PhysioDesigner 1.0](#) is available. PhysioDesigner can embed CellDesigner's SBML model into its multilevel physiological PHML model. (2014/08/01)

[CellDesigner 4.4](#) is now available (2014/07/12)

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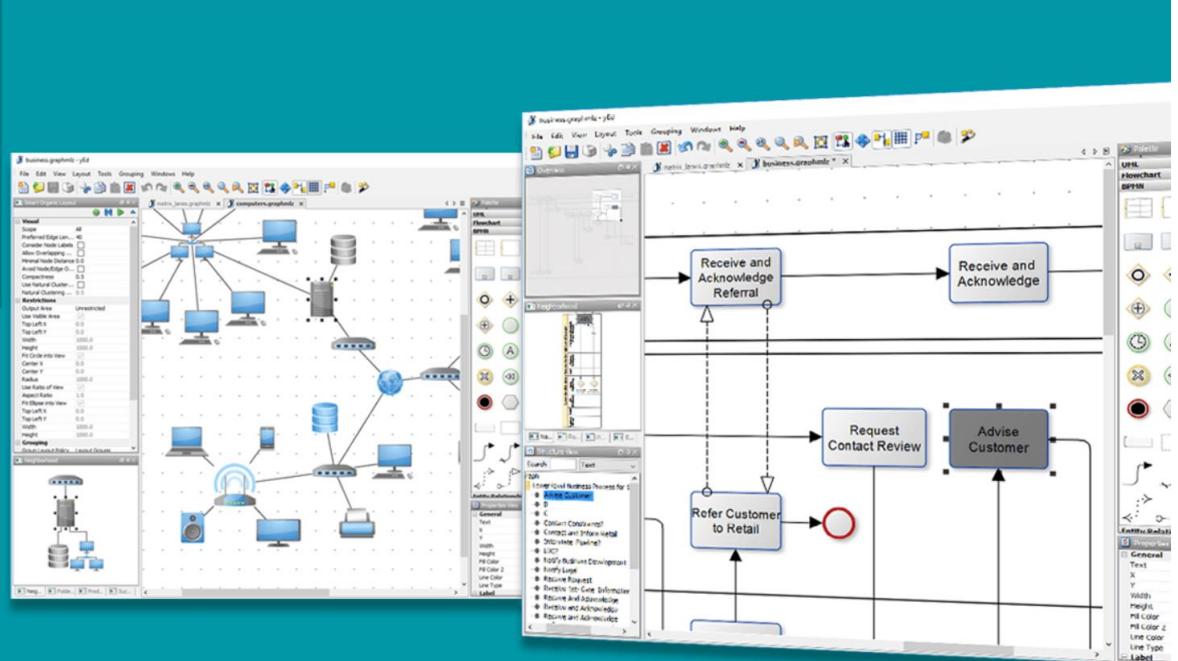


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Welcome to Newt Pathway Viewer & Editor

Newt is a free, web based, open source viewer and editor for pathways in [Systems Biological Graphical Notation \(SBGN\)](#) and [Simple Interaction Format \(SIF\)](#). It was written with a series of libraries and extensions based on [Cytoscape.js](#) with utmost customization in mind.

[Launch **newt**](#)

What distinguishes Newt from other viewers and editors for biological maps can be summarized as:

Search

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Latest News

Newt release

April 1, 2020

Newt 3.0 was released to include some [new features](#) such as

Prerequisites for high-quality biochemical interaction maps:

- **Accurate** – correctly represents our empirical knowledge.
- **Reusable** – well annotated and referenced.
- **Comprehensive** – accounts for all known reactions within the selected scope.
- **Machine readable** – can be processed and analyzed using computers.

-
- **Executable** – corresponds to a computational model that can be simulated.
 - **Functional** – can explain the known system-level behavior of the biological network.

(Inspired by *Systems Biology*, ed. Nielsen and Hofmann, Chapter 8, Wiley -VCH, 2016 and *Community-driven roadmap for integrated disease maps*, Ostaszewski et al., 2018)



Adding a dynamical layer

“Why build models?” Jay Bailey

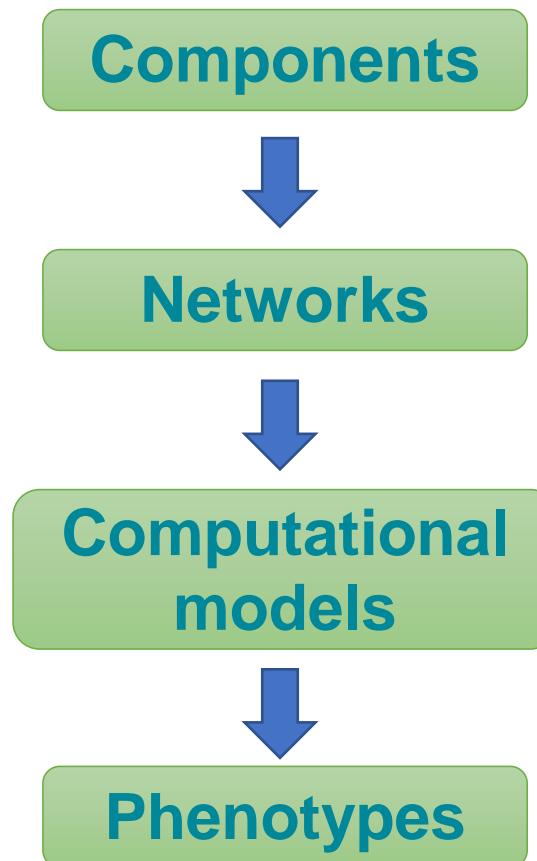
- To organize disparate information into a coherent whole.
- To think (and calculate) logically about what components and interactions are important in a complex system.
- To discover new strategies.
- To make important corrections to the conventional wisdom.
- To understand the essential qualitative features.



Computational models

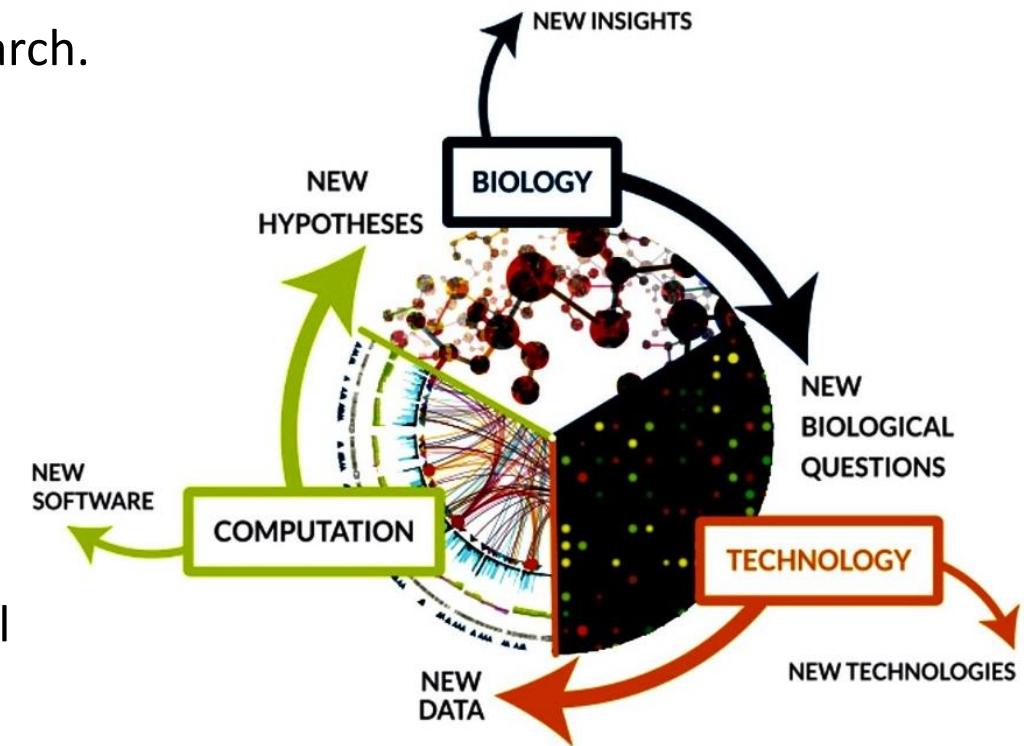
- Models are used to represent actual quantitative/qualitative relations between the molecules in the system.
- Abstract representations of biological processes
- Have an inherent execution scheme attached to the model.

Central dogma of computational systems biology



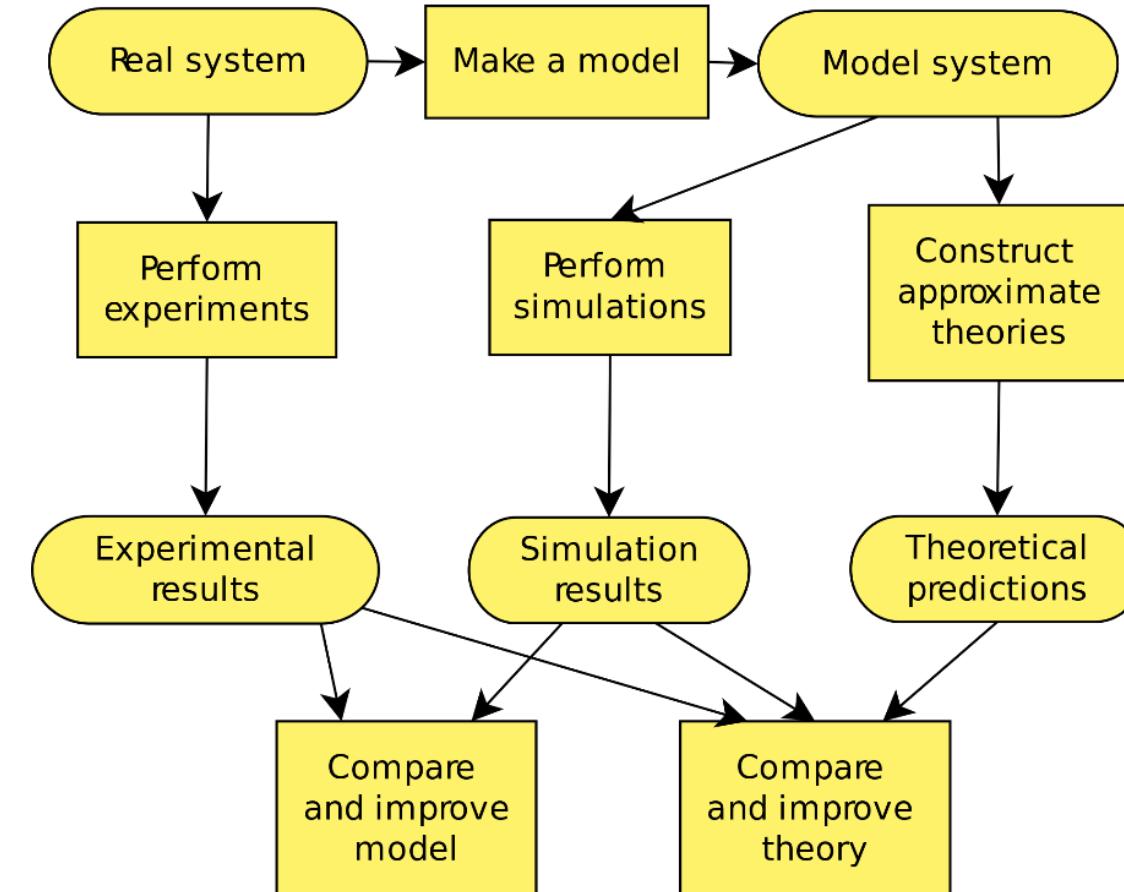
Model building: a step by step process

- Generation of the structural model based on a literature search.
- Compilation of a calibration dataset using experimentally validated biological knowledge.
- Model fitting to the experimental data.
- *In silico* simulations to generate predictions.
- Validation of predictions through experimental testing.
- Model refinement by feeding newly generated experimental data back to the model.
- Generation of novel hypotheses.
- Reiteration.



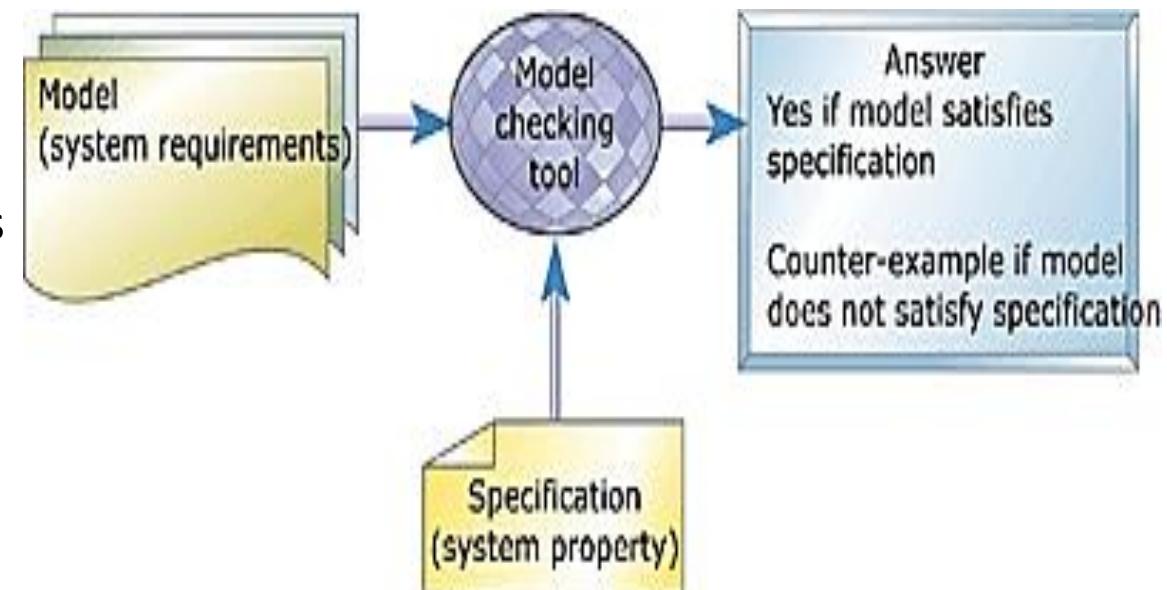
“In theory, there is no difference between theory and practice.

But in practice, there is.” “The Yale Literary Magazine”, February 1882; Benjamin Brewster



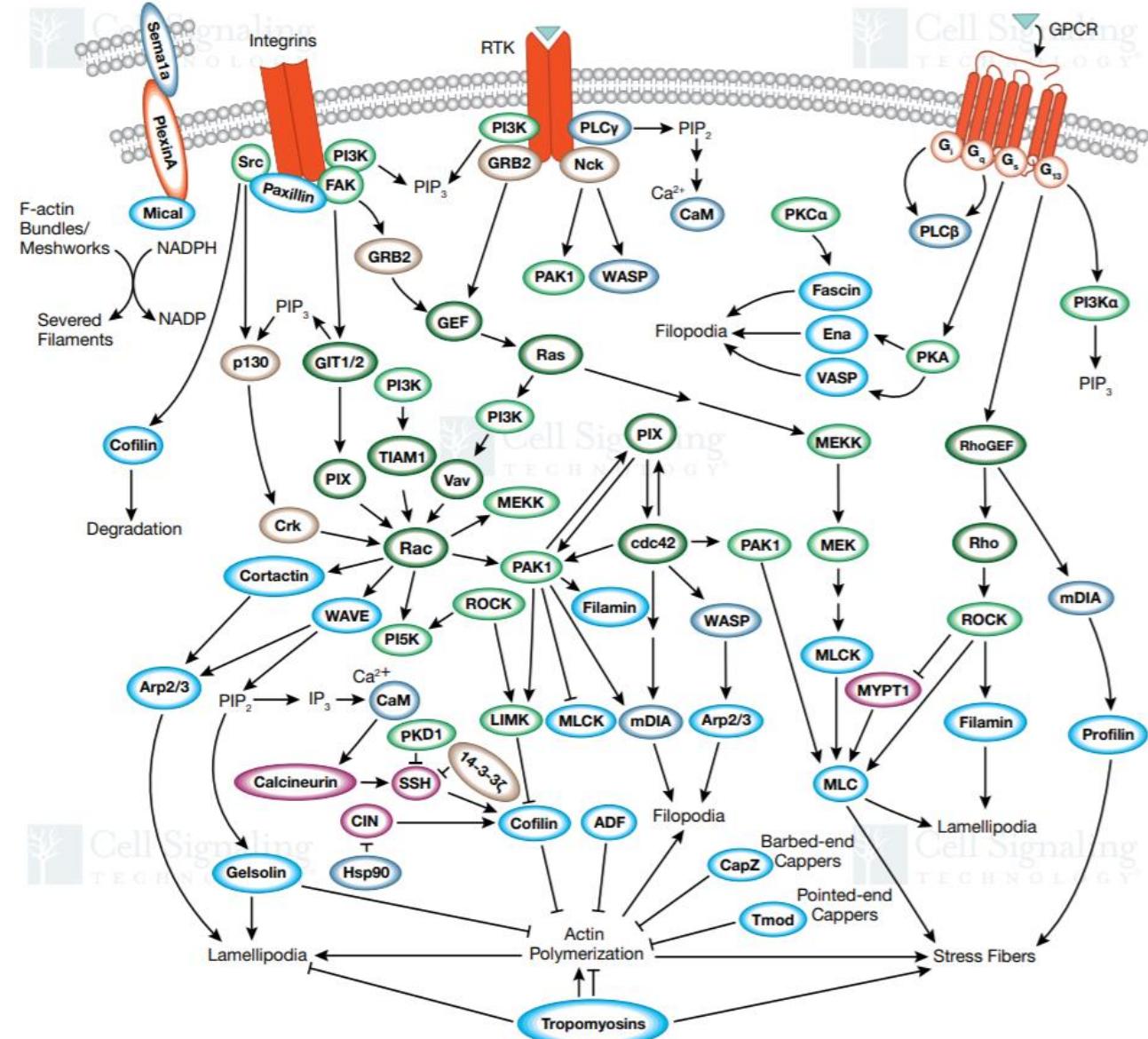
Model checking techniques - Comparing mechanistic models to specifications

- A formal model of the system under study is constructed.
- Experimental evidence is formalized as specifications (observations).
- Model checking is used to ensure that the model reproduces the experimental observations.
- **Mismatch with experimental observations:** model should be refined by additional information.
- **Match with experimental observations:** could lead to further querying and testing of the model to suggest further experimental studies.



Reachability analysis

- Extra-cellular molecules trigger a response inside the cell by initiating a signal at special membrane receptors.
- Signal is transmitted to reporters/ targets through various chains of interactions among proteins.
- Understanding whether such a signal can reach from membrane receptors to reporters is essential in studying the cell response to extra-cellular events.



COMPUTATIONAL (BIO) MODELING METHODOLOGIES → LEARNING METHODOLOGIES

Hypothesis-driven

(Mostly) Data-driven

PROCESS ALGEBRA An example in Beta Binder $((\beta(x, \Delta_E)[E]) \parallel (\beta(y, \Delta_I)[I]))$ \downarrow join operator $\beta^h(x, \Delta_E)\beta^h(y, \Delta_I)(E \parallel I)$ $\beta(\cdot)$ active binding site $\beta^h(\cdot)$ hidden binding site \parallel parallel operator Enzyme (E) Inhibitor (I)	RULE-BASED SYSTEMS $EGFR(ECD1, aa1092-Y).EGFR(ECD1, aa1092-Y)$ \downarrow $EGFR(ECD1, aa1092-pY).EGFR(ECD1, aa1092-Y)$ (An example in BioNetGen)	PETRI NETS PLACE TRANSITION NOT ENABLED TOKEN TRANSITION ENABLED	SUPERVISED LEARNING Advantages: <ul style="list-style-type: none"> Data transformations learnt during training Issues: <ul style="list-style-type: none"> Typically many parameters → overfitting Difficult to map results back to informative features 																		
LOGIC-BASED $r1(brt2.1) \stackrel{\text{def}}{=} \forall t, n. T(t) \otimes C(n, breast, 1, [TGF\beta]) \rightarrow T(t + d_{11}(f)) \otimes A(n), f \in 0..2 =$ 	FLUX BALANCE + OPTIMISATION 	CONTINUOUS TIME AND HIDDEN MARKOV CHAINS 	VARIATIONAL AUTOENCODER (VAE) probabilistic framework 																		
LATTICE-BASED 	CHEMICAL MASTER EQUATION 	AGENT-BASED 	UNSUPERVISED LEARNING Unsupervised neural models developed: <ul style="list-style-type: none"> DIFVAE Disentangled-DIFVAE Graph-DIFVAE $q_\phi(z x) = \mathcal{N}(z; \mu, \text{diag}(\sigma^2))$ $p_\theta(x z) = \prod_{i=1}^n p_\theta(x_i z) = \prod_{i=1}^n x_i^{z_i} (1 - x_i)^{1-z_i}$																		
ORNSTEIN-UHLENBECK Branching Phylogeny 	COMPLEX NETWORKS 	GAME THEORY Player 1 <table border="1"> <tr> <td></td> <td>-</td> <td>-</td> </tr> <tr> <td>-</td> <td>+</td> <td>-</td> </tr> <tr> <td>+</td> <td>+</td> <td>-</td> </tr> </table> Player 2 <table border="1"> <tr> <td></td> <td>-</td> <td>-</td> </tr> <tr> <td>-</td> <td>Altruism</td> <td>Spite</td> </tr> <tr> <td>+</td> <td>Cooperation</td> <td>Selfishness</td> </tr> </table>		-	-	-	+	-	+	+	-		-	-	-	Altruism	Spite	+	Cooperation	Selfishness	BAYESIAN LEARNING $\ell(\beta_Z) = \arg \min_{\beta_Z} \left(\sum_{i=1}^n \delta_i \left\{ \mathbf{x}_{Z,i}^T \beta_Z - \log \left[\sum_{j \in R(i)} \exp(\mathbf{x}_{Z,j}^T \beta_Z) \right] \right\} + P_\lambda(\beta_Z) \right)$ Network-based Cox Regression models
	-	-																			
-	+	-																			
+	+	-																			
	-	-																			
-	Altruism	Spite																			
+	Cooperation	Selfishness																			
			REINFORCEMENT LEARNING 																		

Interpretability/ non linearity/parameter estimation

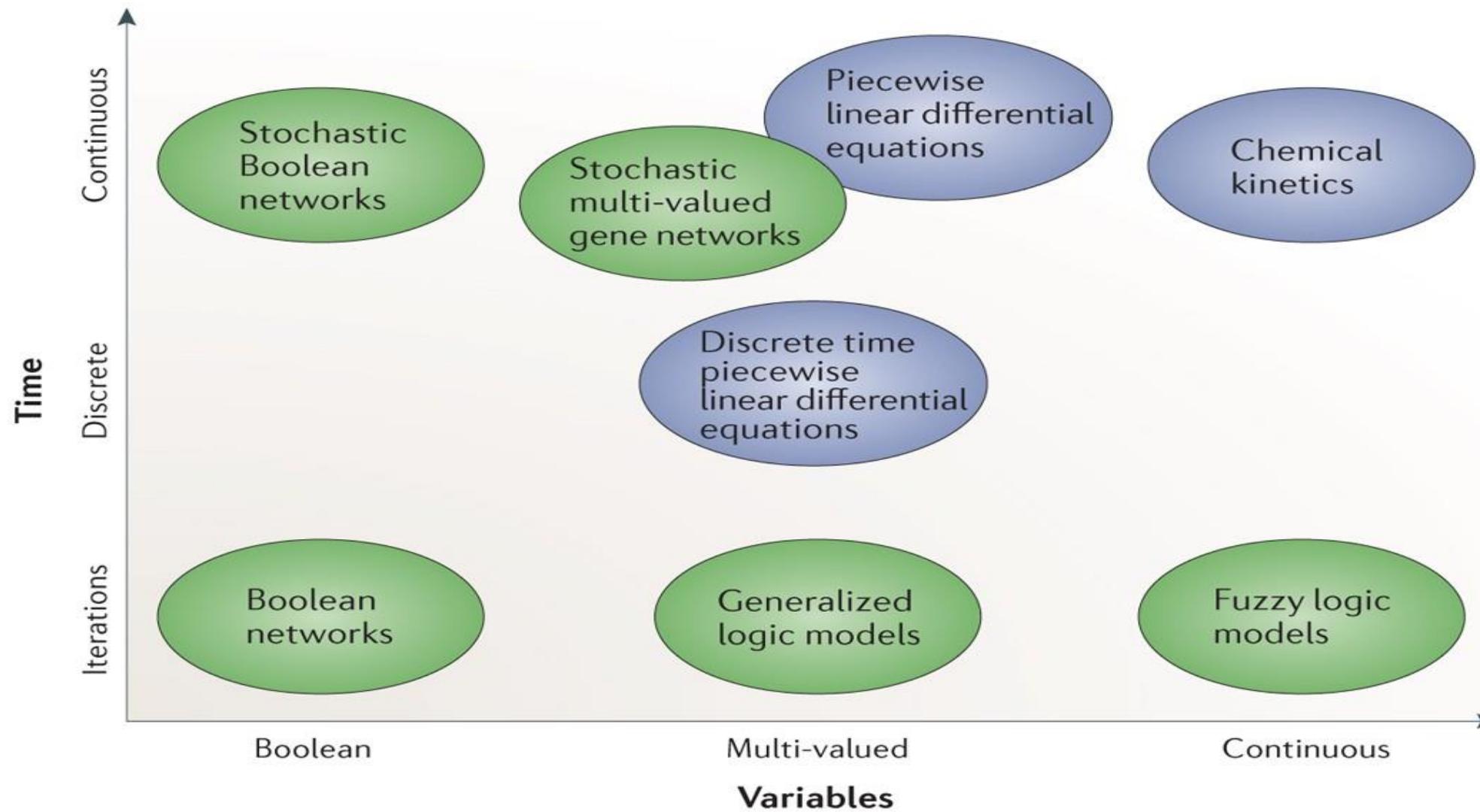
Quantitative versus qualitative models

Table 1

Comparison matrix of quantitative and qualitative models

	Quantitative model	Logic model
Suitable for	Time series	Phenotypes
Time representation	Linear representation	Abstract iterations
Variables	Quantitative	Qualitative
Mechanism representation	Yes	No
What can we do?	Compute concentrations and durations; evaluate the effect of parameter values	Compute state transitions and attractors (steady-states and cyclic attractors)
Data necessary to build the model	Molecular species, genes, interactions, biochemical processes	Activities, defined phenotypes, rules linking those
Data to parameterize and validate the model	Amount of molecular species, timecourses, quantitative phenotype	Perturbations of activities such as RNA interference, inhibitors, qualitative phenotypes
Advantages	Quantitative, precise; direct comparison with quantitative measurements; large existing toolkit	Easy to build; easy to compose; easy simulation of perturbations
Weaknesses	Requires quantitative knowledge of initial conditions and kinetics	Cannot provide quantitative predictions; difficult to choose between alternative behaviours

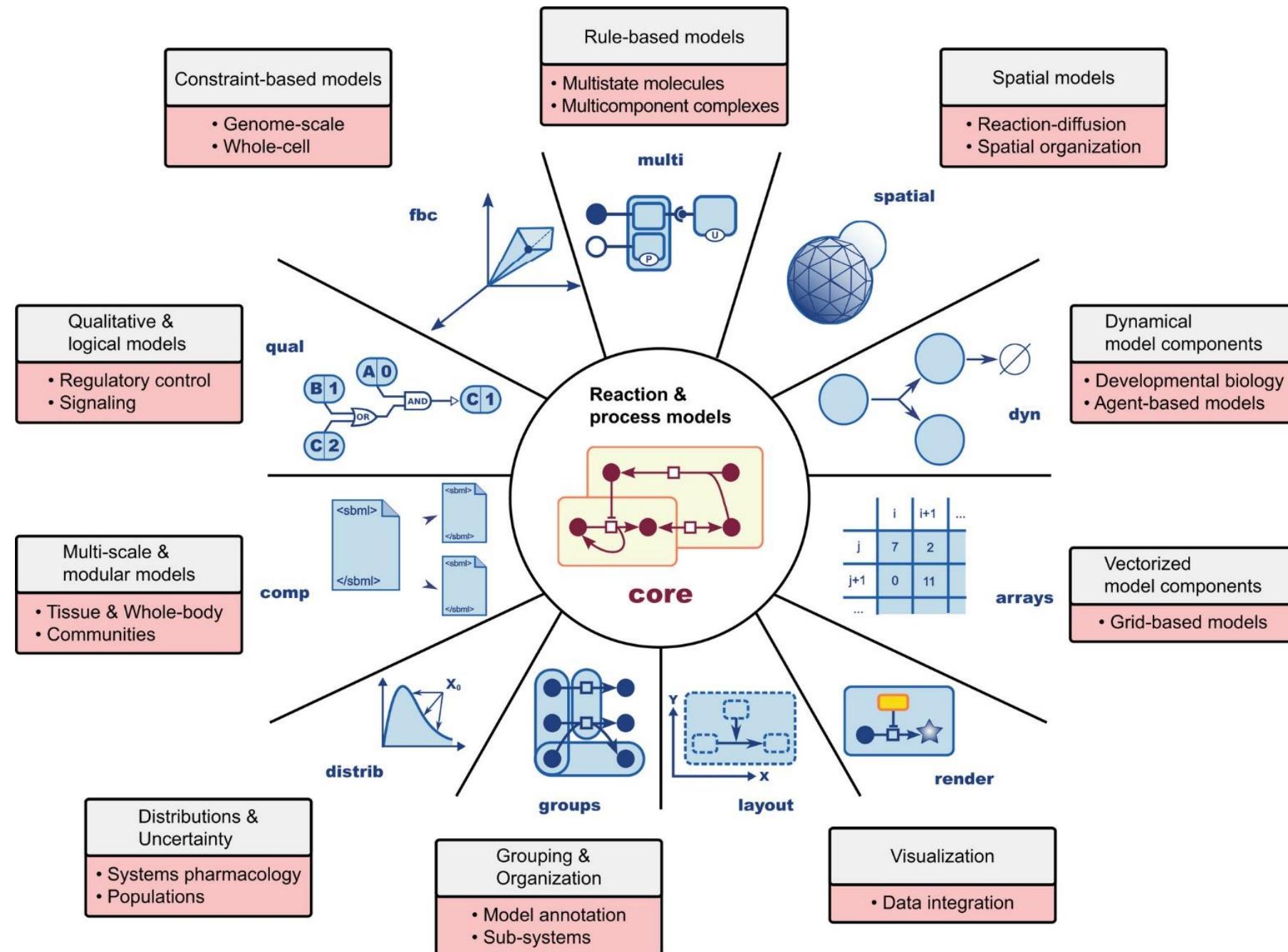
Granularity of time representation and variable values for various modelling approaches.



Many different modelling approaches – one common language?



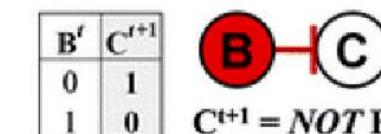
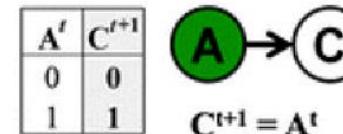
- A format to encode mathematical models that is used in systems biology.
- Initially focused on non-spatial, reaction-based biochemical models.
- Packages covering different modelling approaches (qual).
- Supported by software libraries in different programming languages .
- Can be imported or exported by a variety of modelling and simulation tools.
- Does not store experimental data, or simulation descriptions.
- Based on xml format, intended to be machine and not human-readable.



Logic-based models

- Form of mathematical model governed by logic operators (AND, OR, NOT).
- Parameter free.
- Suitable for modeling gene regulatory networks.
- In silico* simulations, qualitative predictions.
- Each node in a logic model has a corresponding logic function that controls its regulation each time the model is updated.
- Two updating schemes: synchronous and asynchronous.

A Logic functions with one molecular regulator

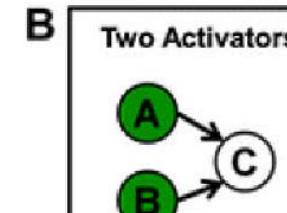


Truth table

Truth table

Logic functions with two molecular regulators

Non-specific Interaction Network



AND C is only ON in one condition

A^t	B^t	C^{t+1}
0	0	0
1	0	0
0	1	0
1	1	1

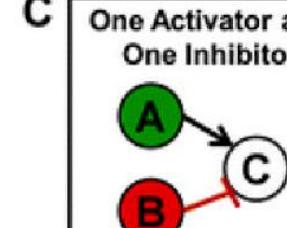
The presence of A and the presence of B activates C.

OR C is only OFF in one condition

A^t	B^t	C^{t+1}
0	0	0
1	0	1
0	1	1
1	1	1

Either the presence A or the presence of B activates C.

C One Activator and One Inhibitor



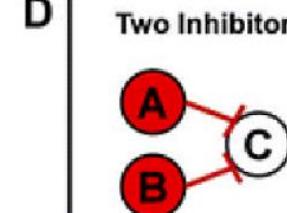
A^t	B^t	C^{t+1}
0	0	0
1	0	1
0	1	0
1	1	0

The presence of A and the absence of B activates C.

A^t	B^t	C^{t+1}
0	0	1
1	0	1
0	1	0
1	1	1

Inhibitor Dominant

D Two Inhibitors



A^t	B^t	C^{t+1}
0	0	1
1	0	0
0	1	0
1	1	0

The absence of A and the absence of B activates C.

A^t	B^t	C^{t+1}
0	0	1
1	0	1
0	1	1
1	1	0

Activator Dominant

Attractors' search: an important aspect of dynamical analysis

- Dynamical analysis can reveal **attractors** (complex or simple) that could correspond to **fixed points** (steady states) or **oscillatory behaviours** (periodic states).
- Attractors represent a stable behaviour of a system, as reflected by a fixed trajectory in the space of all possible states of the system.